(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/032273 A1

(51) International Patent Classification:
C07D 417/04 (2006.01) *A61P 25/16* (2006.01)
C07D 417/14 (2006.01) *A61P 25/18* (2006.01)
A61K 31/427 (2006.01) *A61P 25/24* (2006.01)
A61P 25/02 (2006.01) *A61P 25/28* (2006.01)

(21) International Application Number:
PCT/DK2005/000591

(22) International Filing Date:
20 September 2005 (20.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/612,236 22 September 2004 (22.09.2004) US
PA 2004 01441 22 September 2004 (22.09.2004) DK

(71) Applicant *(for all designated States except US)*: **H. Lundbeck A/S** [DK/DK]; Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LARSEN, Mogens** [DK/DK]; Tulipanhaven 30, DK-2765 Smørum (DK). **SAMS, Anette, Graven** [DK/DK]; Jakob Dannefærds Vej 4a, 1., DK-1973 Frederiksberg C (DK). **MIKKELSEN, Gitte** [DK/DK]; Skovbovænget 143, DK-2750 Ballerup (DK). **BANG-ANDERSEN, Benny** [DK/DK]; Lillegrund 33, DK-2300 Copenhagen S (DK).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/032273 A1

(54) Title: 2-ACYLAMINOTHIAZOLE DERIVATIVES

(57) Abstract: The Invention relates to compounds of the formula I, wherein the variables are as defined in the claims, for use as a medicament. The compounds are A_{2A}-receptor legends and are useful in the treatment of neurological and psychiatric disorders where an A_{2A}-receptor is implicated.

2-Acylaminothiazole derivatives

Field of the Invention

The compounds of the present invention belong to a novel class of 2-acylaminothiazole derivatives having affinity for the adenosine 2A (A_{2A}) receptor. The compounds are A_{2A}-receptor ligands, such as antagonists, agonists, reverse agonists or partial agonists, and are useful in the treatment of neurological and psychiatric disorders where an A_{2A}-receptor is implicated. Examples of diseases where an A_{2A}-receptor is implicated are Parkinson's Disease (PD), Alzheimer's Disease, Huntington's disease, cerebral ischemia, haemorrhagic stroke, neonatal ischemia and hypoxia, subarachnoid haemorrhage, traumatic brain injury, cardiac arrest, Multiple Sclerosis, depression and psychosis.

Background of the invention

Adenosine is present in all cells, including neurons and glia, of mammalian organisms where it modulates a variety of important physiological processes. The action of adenosine is mediated by specific receptors, which belong to the family of G protein-coupled receptors. Four adenosine receptors have been cloned and characterized, A_1, A_{2A}, A_{2B} and A_3 (Fredholm et al, **1994**, *Pharmac. Rev.*, 46, 143-156). The main intracellular signaling pathways involve the formation of cAMP, with A_1 and A_3 receptors causing inhibition of adenylate cyclase and A_{2A} and A_{2B} receptors activating it (Olah et al, *Pharacol. Ther.*, **2000**, 85, 55-75).

All of the adenosine receptors have been located in the CNS (Impagnatiello et al, *Emerg. Ther. Targets*, **2000**, 4, 635-644; Rosin et al, *J. Comp. Neurol.*, **1998**, 401, 163-186). The receptor of interest here, A_{2A}, is predominantly found in dopamine-rich areas, such as the basal ganglia components; the striatum and the globus pallidus, in various mammalians, including humans. The basal ganglia, with the striatum as a central component, are involved in integration of cortical, thalamic and limbic information to produce motor behaviours (for review see Svenningson et al, *Prog. Neurobiol.*, **1999**, 59, 355-396).

In the striatum A_{2A} and dopamine D_2 receptors are found closely co-localized on the striatopallidal GABAergic neurons, forming the so-called indirect output pathway from the striatum, which is involved in motor inhibition. A_{2A} receptors contribute to control of motor behaviour by modulating the neurotransmission of GABA, dopamine, acetylcholine and glutamate in various ways. Currently, the interactions between A_{2A} and D_2 receptors, and especially the actions of A_{2A} antagonists, is of great interest in the treatment for Parkinson´s disease (PD). The A_{2A} receptors interact tonically and antagonistically with the D_2 receptors, causing a decrease in affinity of the D_2 receptors for dopamine upon stimulation. Thus, A_{2A} antagonists may be capable of enhancing the effect of endogenous dopamine as well as clinically used dopamine agonists and increase the time-period of dopaminergic drug response. (For details and references therein see e.g: Richardson et al, *Trends Pharmacol. Sci.*, **1997**, 18, 338-344; Svenningson et al, *Prog. Neurobiol.*, **1999**, 59, 355-396; Fuxe et al, *Parkinson´s Dis. Adv.*, **2001**, 86, 345-353).

Selective A_{2A} receptor agonists and antagonists have been widely described in pharmacological, behavioural and neuroprotective experiments in rodents and non-human primates (for reviews see: Richardson et al, *Trends Pharmacol. Sci.*, **1997**, 18, 338-344; Ribeiro et al, *Prog. Neurobiol.*, **2003**, 68, 377-392; Ongini et al, *Il Farmaco*, **2001**, 56, 87-90; Wardas, *Polish J. Pharmacology*, **2003**, 54, 313-326).

The close interaction of D_2 and A_{2A} receptors can be clearly exemplified in models of catalepsy, where D_2 receptor antagonists as well as A_{2A} receptor agonists induce catalepsy, which is counteracted by A_{2A} receptor antagonists and D_2 receptor agonists, respectively (see Svenningson et al, *Prog. Neurobiol.*, **1999**, 59, 355-396 and references therein).

Promising anti-parkinsonian effects of A_{2A} receptor antagonists have currently been reported by many investigators. For example, both SCH58261 (2-(2-furanyl)-7-(2-phenylethyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine) and KW-6002 (8-[(1E)-2-(3,4-dimethoxyphenyl)ethenyl]-1,3-diethyl-3,7-dihydro-7-methyl-1*H*-purine-2,6-dione), enhance contralateral rotations, elicited by a

subtreshold dose of levodopa, in unilateral 6-OHDA (6-hydroxydopamine) lesioned mice and rats (See Ongini et al, *Drug Dev. Res.*, **2001**, 52, 379-386 and references therein). Furthermore, KW-6002 significantly improves motor impairment induced in non-human primates by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), without causing dyskinesias, that is commonly described for long-term treatment with the dopamine agonist L-dopa (Kanda et al, *Ann. Neurol.*, **1998**, 43, 507- 513; Grondin et al, Neurology, **1999**, 52, 1673-1677; Kanda et al, *Exp. Neurol.*, **2000**, 162, 321-327).

Thus, A_{2A} receptor antagonists show great potential as future drugs for long-term medication of PD patients, since they do not only reverse the motor impairment but also can slow down or stop the progress of the disease by promoting cell survival.

Neuroprotective effects by A_{2A} receptor antagonists have recently been reported in *in vivo* and *in vitro* models of different neurodegenerative diseases (for review see: Wardas J., *Pol. J. Pharmacol.* **2002**, 54, 313-26 and Stone TW. *Adv. Exp. Med. Biol.* **2002**, 513, 249-80). A_{2A} antagonists have been shown to be neuroprotective in different PD models like in MPTP treated mice and 6-OHDA-lesioned rats. Here, KW-6002 prevented functional loss of dopaminergic nerve terminals in the striatum as well as prevented gliosis normally induced around degenerating neurons (Ikeda et al, *J. Neurochem.*, **2002**, 80, 262-270; Hirsch et al, *Adv. Neurol.*, **1999**, 80, 9-18; Kanda et al, *Ann. Neurology*, **2000,** 43 (4), 507-513, Lundblad et al. *J. Neurochem.* **2003**, 84(6), 1398-410). Similar results have been obtained in experimental models of Huntington's disease (HD). In rat HD models quinolinic acid or kainate induced lesions were reduced after using adenosine A_{2A} receptor antagonists, with a decrease in striatal cell loss and motor changes (Reggio et al, *Brain Res.* **1999**, 831, 315-318; Popoli et al, *J. Neurosci.*, **2002**, 22, 1967-1975). In addition, it has been shown that A_{2A} receptor antagonists decrease neuronal cell death after cerebral ischemia in neonatal and adult rats and gerbils (Gao Y, Phillis JW., *Life Sci.* **1994**, 55(3), PL61-5; Monopoli A. et al, *Neuroreport*, **1998**, 9(17), 3955-9). A_{2A} knock out animals have been reported to be protected from neonatal hypoxic ischemia and transient focal ischemia (Bona E. et al, *Neuropharmacology*, **1997,** 36(9), 1327-38; Chen JF. et al, *J Neurosci,* **1999,** 19(21), 9192-9200) and from 3NP (3-nitropropionic acid) induced,

presynaptic, neurotoxic glutamate release (Blum D. et al, *J. Neurosci*, **2003**, 23, 5361-5369). The protective effect of A_{2A} antagonists against neurodegeneration by glutamate release have allready been shown in a rat model of ischemic damage to the cerebral cortex (Simpson RE, *J Neurochem*, **1992,** 58, 1683-1690 and O'Regan MH. et al, Brain Res, **1992,** 582, 22-26).

Protection by A_{2A} antagonists has also been reported in primary astrocytes, in a rat model of bFGF induced astrogliosis, an amyloid beta peptide 25-35 induced neurotoxicity in cerebral granule cells (CGCs) and model of QA induced neuronal cell death in rat organotypic slice cultures (Brambilla R. et al. *Glia.* **2003**, 43,190-194; Dall'Igna OP. et al. *Br. J. Pharmacol.* **2003**, 138:1207-1209; Tebano MT,. et al. *Eur. J. Pharmacol.* **2002**, 253-257)

Collectively, A_{2A} receptor antagonists can efficiently protect different neurons from various forms of insult induced neurodegeneration (Abbracchio MP, Cattabeni F **1999** *Ann. NY Acad. Sci.* 890: 79-92; Ongini E. et al, *Ann. NY Acad. Sci.*, **1997,** 825: 30-48).

Adenosine and its analogues induce "depressant-like" effects in animal models of psychiatric disorders (Minor et al., *Behav. Neurosci.,* **1994**, 108: 265-276; Woodson et al., *Behav. Neurosci.* **1998**, 112: 399-409). Moreover, these behavioural deficits were found to be reversed by adenosine A_{2A} receptor antagonists (Minor et al., *Behav. Brain Res.* **2001**, 120, 230-212). Further studies have shown that treatment with adenosine or 2-chloroadenosine increased immobility time in the mouse forced swimming test, another animal model of depression generally considered reliable (Porsolt et al., *Arch. Int. Pharmacodyn. Ther.,* **1977**, 229: 327-336).

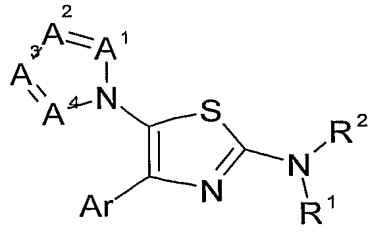
Several compounds with dual affinity for A_{2A} and A_1 receptor subtypes, known as the 4-amino[1,2,3]triazolo[4,3-*a*]quinoxalines, has been shown to be active in the rat forced swimming test (Sarges et al., *J. Med. Chem.,* **1990**, 33, 2240-2254) indicating antidepressant activity of the substances. Most recently, A_{2A} receptor knockout mice were found to be less sensitive to "depressant" challenges than their wildtype littermates (El Yacoubi et al., *Br. J. Pharmacol.* **2001**, 134, 68-77). Consistent with

this data, the A_{2A} receptor antagonists SCH58261 and KW6002 reduced the total immobility time in the mouse tail suspension test (El Yacoubi et al., *Br. J. Pharmacol.* **2001**, 134, 68-77). The antagonists SCH58261 and ZM241385 4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo[2,3-*a*][1,3,5]triazin-5-ylamino]-ethyl)phenol were also found to reduce immobility when administered to mice previously screened for having high immobility time, while SCH58261 reduced immobility of mice that were selectively bred for their "helplessness" in this model (El Yacoubi et al., *Br. J. Pharmacol.* **2001**, 134, 68-77).

Studies using A_{2A} knockout mice suggest that these animals show a blunted response to psychostimulants such as amphetamine and cocaine, despite the fact that their expression and binding affinities of D1 and D2 receptors are unaffected (Chen et al., *Neurosci.*, **2000**, 97, 195-204). Moreover, inactivation of A_{2A} receptors has been shown to selectively attenuate amphetamine-induced behavioural sensitisation (Chen et al., *Neuropsychopharmacol.*, **2003**, 28, 1086-1095). In addition, A_{2A} knockout mice show reduced startle and PPI of the acoustic startle (Wang et al., *Behav. Brain Res.*, **2003**, 143, 201-207), measures often used to detect antipsychotic activity. Further support is found in studies where pharmacological blockade of A_{2A} receptors with a selective antagonist completely abolished pre-pulse imhibition (PPI) (Nagel et al., *Synapse*, **2003**, 49, 279-286). Psychostimulants, such as MK-801 and amphetamine failed to disrupt startle and PPI in A_{2A} KO mice (Wang et al., *Behav. Brain Res.*, **2003**, 143, 201-207).

Thus, the available evidence suggests that adenosine A_{2A} receptor antagonists, by specifically modulating mesostriatal or mesocorticolimbic dopaminergic pathways, may possess antidepressant and/or antipsychotic properties

WO02/42298 discloses compounds of the formula:



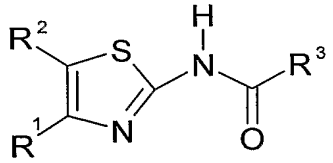
as A_{2B} receptor antagonists which in general selectively inhibit activation of the A_{2b} receptor over the adenosine A_1 and A_{2A} receptors. The compounds are disclosed as being useful in the treatment of inflammatory or obstructive airways diseases.

Hence, there is a desire for novel A_{2A}-receptor ligands, such as antagonists, agonists, reverse agonists or partial agonists.

Summary of the Invention

The objective of the present invention is to provide compounds that are A_{2A}-receptor ligands, such as antagonists, agonists, reverse agonists or partial agonists.

Accordingly, the present invention relates to compounds of formula I



I

wherein R^1 is phenyl, thien-2-yl or thien-3-yl, wherein each phenyl and thienyl optionally are substituted with one or more substituents selected from halogen, C_{1-6}-alkyl and C_{1-6}-alkoxy;

R^2 is a five membered heteroaryl selected from the group consisting of furan-2-yl, furan-3-yl, [1,2,4]-oxadiazol-3-yl, [1,2,4]-oxadiazol-5-yl, [1,2,5]-oxadiazol-3-yl, [1,2,4]-thiadiazol-3-yl, [1,2,4]-thiadiazol-5-yl, [1,2,5]-thiadiazol-3-yl, wherein the heteroaryl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkoxy-C_{1-6}-alkyl, or R^2 is tetrazol-5-yl substituted in the 1 or 2-position with C_{1-6}-alkyl or phenyl-C_{1-6}-alkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl, or R^2 is 5-oxo-4,5-dihydro-[1,3,4]-oxadiazol-2-yl;

and R^3 is selected from the group consisting of C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, furanyl, furanyl-C_{1-6}-alkyl, thienyl, thienyl-C_{1-6}-alkyl, phenyl, phenyl-C2-6-alkene and phenyl-C_{1-6}-alkyl wherein the phenyl-C_{1-6}-alkyl optionally is substituted in the phenyl ring with one or more substituents selected from halogen, C_{1-6}-alkyl and C_{1-6}-alkoxy;

for use as a medicament.

In a second aspect the present invention relates to the use of compounds of formula I as defined above for the manufacture of a medicament for treatment of a disease where an A_{2A}-receptor is implicated.

In a third aspect the present invention relates to compounds of formula I as defined above provided that the compound is not N-[5-(5-nitro-furan-2-yl)-4-phenyl-thiazol-2-yl]-benzamide.

The compounds of the invention are A_{2A}-receptor ligands, such as antagonists, agonists, reverse agonists or partial agonists having a human A_{2A} binding affinity (K_i) of 5 μM or less, typically of 1 μM or less, preferably of 550 nM or less, more preferred of 200 nM or less, even more preferred of 50 nM or less and most preferred of 10 nM or less.

Detailed Description of the Invention

In a particular embodiment the present invention relates to use of compounds of formula I as defined above for the manufacture of a medicament for the treatment of a disease where an A_{2A}-receptor is implicated, is selected from the group consisting of Parkinson's Disease, Alzheimer's Disease, Huntington's disease, cerebral ischemia, haemorrhagic stroke, neonatal ischemia and hypoxia, subarachnoid haemorrhage, traumatic brain injury, cardiac arrest, Multiple Sclerosis, depression and psychosis.

In a more particular embodiment the present invention relates to use of such compounds for the manufacture of a medicament for the treatment of Parkinson's Disease.

In a particular embodiment the present invention relates to such compounds which are A_{2A}-receptor antagonists.

In another particular embodiment the compounds are selective ligands to the A_{2A} receptor over the A_1 or A_{2B} receptors. In a more particular embodiment the compounds are selective ligands to the A_{2A} receptor over the A_1 receptor. In an equally particular embodiment the compounds are selective ligands to the A_{2A} receptor over the A_{2B} receptor.

In a particular embodiment the present invention relates to compounds of formula I as defined above wherein R^1 is phenyl.

In another particular embodiment the present invention relates to compounds of formula I as defined above wherein R^1 is thien-2-yl.

In another particular embodiment the present invention relates to compounds of formula I as defined above wherein if R^2 is a tetrazol-5-yl, then it is substituted in the 2-position.

In another particular embodiment the present invention relates to compounds of formula I as defined above wherein if R^2 is a tetrazol-5-yl, then it is substituted in the 1-position.

In a more particular embodiment the present invention relates to compounds of formula I as defined above wherein if R^2 is a tetrazol-5-yl, then it is substituted with methyl, ethyl, propyl, butyl, isobutyl, cyclopropanmethyl or phenethyl.

In another particular embodiment the present invention relates to compounds of formula I as defined above wherein R^2 is furan-2-yl or furan-3-yl, wherein the

heteroaryl is optionally substituted with on or more substituents selected from the group consisting of C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkoxy-C_{1-6}-alkyl.

In another particular embodiment the present invention relates to compounds of formula I as defined above wherein R^2 is [1,2,4]-oxadiazol-3-yl, wherein the heteroaryl is optionally substituted with on or more substituents selected from the group consisting of C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkoxy-C_{1-6}-alkyl.

In another particular embodiment the present invention relates to compounds of formula I as defined above wherein R^2 is [1,2,4]-oxadiazol-5-yl, wherein the heteroaryl is optionally substituted with on or more substituents selected from the group consisting of C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkoxy-C_{1-6}-alkyl.

In another particular embodiment the present invention relates to compounds of formula I as defined above wherein R^2 is [1,2,5]-oxadiazol-3-yl, wherein the heteroaryl is optionally substituted with on or more substituents selected from the group consisting of C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkoxy-C_{1-6}-alkyl.

In another particular embodiment the present invention relates to compounds of formula I as defined above wherein R^2 is 5-oxo-4,5-dihydro-[1,3,4]-oxadiazol-2-yl.

In a particular embodiment the present invention relates to compounds of formula I as defined above wherein R^3 is selected from the group consisting of C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkylmethyl, furan-2-yl, furan-3-yl, thien-2-yl, thien-2-yl-methyl, thien-3-yl, phenylmethyl, phenethylene and benzyl optionally substituted in the phenyl ring.

In a more particular embodiment the present invention relates to compounds of formula I as defined above wherein the benzyl is substituted with one or two methoxy groups in the phenyl ring.

In an equally particular embodiment the present invention relates to compounds of formula I as defined above wherein the benzyl is substituted in the 3 and/or 4 position of the phenyl ring, for use as a medicament.

In a particular embodiment the present invention relates to compounds of formula I as defined above selected from the group consisting of:

2-(3,4-Dimethoxy-phenyl)-*N*-[5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,

2-(3,4-dimethoxy-phenyl)-*N*-(5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-acetamide,

N-(5-furan-3-yl-4-phenyl-thiazol-2-yl)-isobutyramide,

cyclopropanecarboxylic acid [5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

furan-3-carboxylic acid [5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

N-[5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,

furan-2-carboxylic acid [5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

cyclohexanecarboxylic acid [5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

2-cyclopentyl-*N*-[5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,

N-[5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,

cyclopropanecarboxylic acid (5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-amide,

thiophene-3-carboxylic acid [5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

2-cyclopentyl-*N*-(5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-acetamide,

furan-3-carboxylic acid [5-(2-phenethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

N-(5-furan-2-yl-4-phenyl-thiazol-2-yl)-isobutyramide,

furan-2-carboxylic acid (5-furan-3-yl-4-phenyl-thiazol-2-yl)-amide,

2-(3,4-dimethoxy-phenyl)-*N*-(5-furan-2-yl-4-phenyl-thiazol-2-yl)-acetamide,

cyclopropanecarboxylic acid (5-furan-3-yl-4-phenyl-thiazol-2-yl)-amide,
2-(3-methoxy-phenyl)-*N*-(5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-acetamide,
2-(3-methoxy-phenyl)-*N*-[5-(2-phenethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
N-(5-furan-2-yl-4-phenyl-thiazol-2-yl)-2,2-dimethyl-propionamide,
N-(5-furan-3-yl-4-phenyl-thiazol-2-yl)-propionamide,
N-[5-(2-phenethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,
N-(5-furan-2-yl-4-phenyl-thiazol-2-yl)-propionamide,
furan-2-carboxylic acid [5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
3,3-dimethyl-*N*-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-butyramide,
cyclopropanecarboxylic acid [5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
2-cyclopentyl-*N*-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
N-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,
3-methyl-*N*-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-butyramide,
N-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,
N-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide,
hexanoic acid [5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
N-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide,
N-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
2,2-dimethyl-*N*-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,
thiophene-3-carboxylic acid [5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
N-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-isobutyramide,
3-methyl-*N*-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-butyramide,
N-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-propionamide,
2-phenyl-*N*-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-acetamide,
N-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-2-thiophen-2-yl-acetamide,
N-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-acetamide,
2,2-dimethyl-*N*-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-propionamide,
thiophene-3-carboxylic acid [4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-amide,
N-[5-(2-butyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,

2-cyclopentyl-*N*-[5-(2-isobutyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
N-[5-(2-isobutyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide,
N-[5-(2-cyclopropylmethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-3-methyl-butyramide,
furan-2-carboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
3,3-dimethyl-*N*-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-butyramide,
N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-benzamide,
N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-benzamide,
N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-benzamide,
cyclopropanecarboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
cyclopropanecarboxylic acid [5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
cyclopropanecarboxylic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide,
cyclopropanecarboxylic acid [5-(5-ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide,
2-cyclopentyl-*N*-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
2-cyclopentyl-*N*-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
2-cyclopentyl-*N*-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide,
2-cyclopentyl-*N*-[5-(5-ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide,
cyclohexanecarboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
cyclohexanecarboxylic acid [5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
cyclohexanecarboxylic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide,
N-[5-(1-methyl-1*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,
N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,

3-methyl-*N*-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-butyramide,
N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-3-methyl-butyramide,
3-methyl-*N*-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-butyramide,
N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,
N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,
N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-propionamide,
N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide,
N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide,
N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide,
N-[5-(5-Oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide,
2-(3,4-dimethoxy-phenyl)-*N*-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-thiophen-2-yl-thiazol-2-yl]-acetamide,
N-[5-(5-ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-3-phenyl-acrylamide,
hexanoic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
hexanoic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide,
N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide,
N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide,
N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide,
N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide,
2,2-dimethyl-*N*-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,
N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2,2-dimethyl-propionamide,
2,2-dimethyl-*N*-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-propionamide,
furan-3-carboxylic acid [5-(2-methyl-2*H*-tetrazol-5-yl)-4-thiophen-2-yl-thiazol-2-yl]-amide,

thiophene-3-carboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
thiophene-3-carboxylic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide.

The compounds of the general formula **I** may exist as optical isomers thereof and such optical isomers are also embraced by the invention. Throughout the specification and claims, reference to specific compounds refers to the racemates unless otherwise indicated.

The term C_{1-6}-alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, and 2-methyl-1-propyl.

The term C_{3-8}-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, etc.

Halogen means fluoro, chloro, bromo or iodo.

As used herein, the term acyl refers to a formyl, C_{1-6}-alkylcarbonyl, arylcarbonyl, aryl-C_{1-6}-alkylcarbonyl, C_{3-8}-cycloalkylcarbonyl or a C_{3-8}-cycloalkyl-C_{1-6}-alkyl-carbonyl group.

The terms C_{1-6}-alkoxy, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, C_{1-6}-alkylamino, C_{1-6}-alkylcarbonyl, and the like, designate such groups in which the C_{1-6}-alkyl, aryl, heteroaryl and the C_{3-8}-cycloalkyl group are as defined above.

The term C_{2-6}-alkene refers to a branched or unbranched alkene group having from two to six carbon atoms inclusive, such as ethylene, 1-propylene, 2-propylene, isopropylene, methylpropylene, 1-butylene, 2-butylene and 3-butylene.

The term furanyl refers to furan-2-yl or furan-3-yl.

The term thienyl refers to thien-2-yl or thien-3-yl.

The term aryl refers to a carbocyclic aromatic group, such as phenyl or naphthyl, in particular phenyl.

The term heteroaryl refers to 5-membered monocyclic rings such as 1*H*-tetrazolyl, 3*H*-1,2,3-oxathiazolyl, 3*H*-1,2,4-oxathiazolyl, 3*H*-1,2,5-oxathiazolyl, 1,3,2-oxathiazolyl, 1,3,4-oxathiazolyl, 1,4,2-oxathiazolyl, 3*H*-1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,4,2-dioxazolyl, 3*H*-1,2,3-dithiazolyl, 3*H*-1,2,4-dithiazolyl, 1,3,2-dithiazolyl, 1,4,2-dithiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1*H*-imidazolyl, 1*H*-pyrazolyl, 1*H*-pyrrolyl, furanyl, thienyl, 1*H*-pentazole; 6-membered monocyclic rings such as 1,2,3-oxathiazinyl, 1,2,4-oxathiazinyl, 1,2,5-oxathiazinyl, 4*H*-1,3,5-oxathiazinyl, 1,4,2-oxathiazinyl, 1,4,3-oxathiazinyl, 1,2,3-dioxazinyl, 1,2,4-dioxazinyl, 4*H*-1,3,2-dioxazinyl, 4*H*-1,3,5-dioxazinyl, 1,4,2-dioxazinyl, 2*H*-1,5,2-dioxazinyl, 1,2,3-dithiazinyl, 1,2,4-dithiazinyl, 4*H*-1,3,2-dithiazinyl, 4*H*-1,3,5-dithiazinyl, 1,4,2-dithiazinyl, 2*H*-1,5,2-dithiazinyl, 2*H*-1,2,3-oxadiazinyl, 2*H*-1,2,4-oxadiazinyl, 2*H*-1,2,5-oxadiazinyl, 2*H*-1,2,6-oxadiazinyl, 2*H*-1,3,4-oxadiazinyl, 2*H*-1,3,5-oxadiazinyl, 2*H*-1,2,3-thiadiazinyl, 2*H*-1,2,4-thiadiazinyl, 2*H*-1,2,5-thiadiazinyl, 2*H*-1,2,6-thiadiazinyl, 2*H*-1,3,4-thiadiazinyl, 2*H*-1,3,5-thiadiazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 2*H*-1,2-oxazinyl, 2*H*-1,3-oxazinyl, 2*H*-1,4-oxazinyl, 2*H*-1,2-thiazinyl, 2*H*-1,3-thiazinyl, 2*H*-1,4-thiazinyl, pyrazinyl, pyridazinyl, pyrimidyl, pyridyl, 2*H*-pyranyl, 2*H*-thiinyl; and to bicyclic rings such as 3*H*-1,2,3-benzoxathiazolyl, 1,3,2-benzodioxazolyl, 3*H*-1,2,3-benzodithiazolyl, 1,3,2-benzodithiazolyl, benzfurazanyl, 1,2,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, 1*H*-benzotriazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, benzoxazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzothiazolyl, 1*H*-benzimidazolyl, 1*H*-indazolyl, 3*H*-1,2-benzoxathiolyl, 1,3-benzoxathiolyl, 3*H*-2,1-benzoxathiolyl, 3*H*-1,2-benzodioxolyl, 1,3-benzodioxolyl 3*H*-1,2-benzodithiolyl, 1,3-benzodithiolyl, 1*H*-indolyl,

2*H*-isoindolyl, benzofuranyl, isobenzofuranyl, 1-benzothienyl, 2-benzothienyl, 1*H*-2,1-benzoxazinyl, 1*H*-2,3-benzoxazinyl, 2*H*-1,2-benzoxazinyl, 2*H*-1,3-benzoxazinyl, 2*H*-1,4-benzoxazinyl, 2*H*-3,1-benzoxazinyl, 1*H*-2,1-benzothiazinyl, 1*H*-2,3-benzothiazinyl, 2*H*-1,2-benzothiazinyl, 2*H*-1,3-benzothiazinyl, 2*H*-1,4-benzothiazinyl, 2*H*-3,1-benzothiazinyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, isoquinolyl, quinolyl, 1*H*-2-benzopyranyl, 2*H*-1-benzopyranyl, 1*H*-2-benzothiopyranyl or 2*H*-1-benzothiopyranyl.

The term *rac* means racemic.

The acid addition salts of the compounds of the invention are pharmaceutically acceptable salts formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

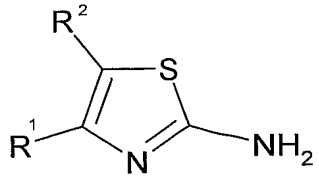
The pharmaceutical compositions of this invention, or those which are manufactured in accordance with this invention, may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 100 mg.

The total daily dose is usually in the range of about 0.05 - 500 mg, and most preferably about 0.1 to 50 mg of the active compound of the invention.

The compounds of the invention are prepared by the following general methods:

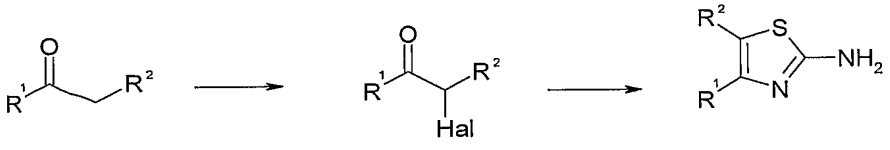
Coupling of a compound with formula II wherein R^1 and R^2 are as described above, with an activated carboxylic acid R^3-COOH or carboxylic acid chloride R^3-COCl or anhydride R^3-CO-O-CO-R^3, wherein R^3 is as defined above.



II

The coupling of compounds of formula II with carboxylic acids, R^3-COOH, is performed by standard procedures known to chemists skilled in the art e.g. in the presence of a carbodiimide coupling reagent at temperatures between 20-80°C in a suitable polar or apolar solvent such as 1-methyl-2-pyrrolidinone or 1,2-dichloroethane, or coupling of a starting material of formula II with carboxylic acid chlorides, R^3-COCl, or anhydrides, R^3-CO-O-CO-R^3, in the presence of a suitable base such as pyridine at temperatures between 20-60 °C in a suitable solvent such as 1,2-dichloroethane.

The compounds of formula II were prepared according to procedures known to chemists skilled in the art or as exemplified in scheme A.



III IV II

Scheme A

Compounds of formula III can be prepared by literature procedures (Aicart et al., J.Heterocycl.Chem., **1985**, 22, 921-925; Chakrasali et al., Synthesis, **1988**, EN; 6, 453-455) or by methods known to the chemist skilled in the art. The furan analogue 3-(2-phenyl-[1,3]dithian-2-ylmethyl)-furan can for example be prepared by

metalation of 2-phenyl-[1,3]dithiane (Kamal et al. *Tetrahedron Lett.* **2002**, 43, 1347) with a suitable metalation agent such as n-butyllithium (Lipshutz et al. *Tett Lett.*, **1990**, 31, 7261) and subsequent reaction with 3-bromomethyl-furan (Mateos et al. *J. Org. Chem.*, **1995**, 60 3580). Deprotection with for example *N*-bromosuccinimide or HgO/$HgCl_2$ will give 3-(2-phenyl-[1,3]dithian-2-ylmethyl)-furan. When R^2 is 1-alkyl tetrazole or 2-alkyl tetrazole, III can be synthesised according to procedures known to chemists skilled in the art. Starting from 3-oxo-3-phenyl-propionitrile, the nitrile can be converted into the tetrazole by standard procedures. This includes the of an azide as sodium azide and triethylammoniumchloride in a suitable solvent e.g. toluene or DMF at temperatures between 80-120°C. Alkylation of the tetrazole by an alkylating agent such as ethylbromide in the presence of a base such as potassium carbonate and a solvent such as acetone at temperatures between 20-80°C gives a mixture of the 2-(1-alkyl-2*H*-tetrazol-5-yl)-1-phenyl-ethanone and 2-(2-alkyl-2*H*-tetrazol-5-yl)-1-phenyl-ethanone. These two compounds can be separated by chromatographic methods.

Compounds of formula III were halogenated α to the carbonyl group by reaction with SO_2Cl_2, Br_2 or I_2 in a suitable solvent such as 1,2-dichloroethane, diethylether or chloroform. The halogenated products (IV) were then ring closed to the aminothiazoles of formula II by reaction with thiourea in a solvent such as ethanol at a suitable temperature e.g. 20-100°C.

Compounds of formula IIa can be prepared from a compound of formula V (Scheme B). Compound V can be prepared by literature procedures (in analogy to compound prepared by Benjamin. et al., *J. Med. Chem.*, **1983**, 26, 100-103) or by the method described above starting from 3-oxo-3-phenyl-propionitrile followed by protection of the amine by a suitable protecting group. 2-Amino-4-phenyl-thiazole-5-carbonitrile can be reacted in a suitable solvent such as ethanol/water with hydroxylamine hydrochlorid in the presence of a suitable base such as potassium or sodium carbonate at a temperature between 50-100°C to give the amidooxime (VI). The 1,2,4-oxadiazoles (VII) can then be prepared by acylation of the amidooxime for example by acid chlorides or acid anhydrides or by reaction with trimethyl- or triethylorthoformate in the presence of a Lewis acid such as BF_3-Et_2O and subsequent

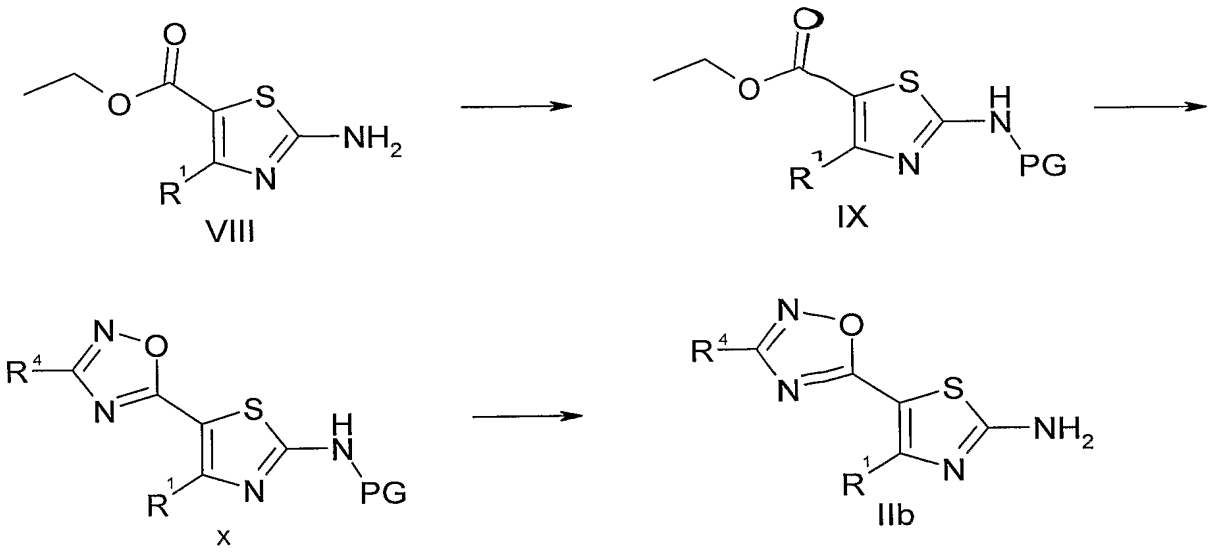
dehydration. Removal of the protecting group gives IIa. Alternatively no protecting group is used and by acylation of the amidooxime (for example by acid chlorides or acid anhydrides or by reaction with trimethyl- or triethylorthoformate in the presence of a Lewis acid such as BF_3-Et_2O and subsequent dehydration) compound VII where PG is the acylgroup from the acid chloride or acid anhydride used. Removal of the protecting group gives IIa.

V VI VII IIa

Scheme B

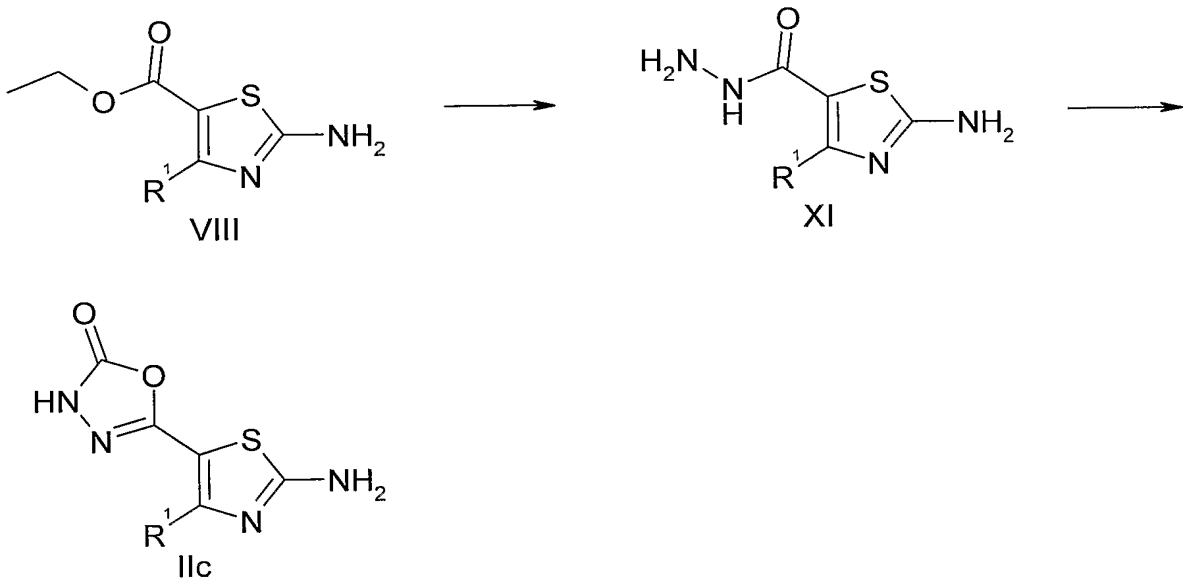
R^4 = alkoxy

Compounds of formula IIb can be prepared from a compound of formula VIII (Scheme C). Compounds of formula VIII can be prepared by literature procedures (in analogy to compound prepared by Choudhari et al. *J. Indian. Chem. Soc.*, **1978**, 55, 401) or by the method described above from compounds of formula II where R2 is an carboxylic acid ester. Protection of the amine by a suitable protection group (PG) as for example boc (t-butoxycarbonyl) will result in the compound IX. The ester can then be converted into the [1,2,4]-oxadialole by my methods known to the chemist skilled in the art, as for example by reaction with amidooximes in presence of a suitable base such as sodium hydride or pyridine at a temperature between 25°C and 100°C. Removal of the protecting group gives IIb.



Scheme C

Compounds of formula IIc can be prepared from compounds of formula VIII (Scheme D). The ester group in the compound of formula VIII can be converted to a hydrazide group by methods known to chemists skilled in the art, as for example by reaction with hydrazine in a suitable solvent such as methanol at a suitable temperature between 25 and 65°C to give a compound of formula XI. The oxadiazolone ring can then be formed by methods known to chemists skilled in the art. This includes reaction of an hydrazide of formula XI with carbonyldiimidazole or carbonyl dichloride in the presence of a suitable base such as triethylamine in a solvent such as tetrahydrofurane and at temperatures between 25 and 50°C.



Scheme D

Experimental Section

Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with an IonSpray source and a Shimadzu LC-8A/SLC-10A LC system. Column: 30 X 4.6 mm Waters Symmetry C18 column with 3.5 µm particle size; solventsystem: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.03); method: Linear gradient elution with 90% A to 100% B in 4 min and with a flow rate of 2 ml/min.

Preparative LC-MS-purification was performed on the same instrument. Column: 10 X 50 mm Waters Symmetry C18 with 5 µm particle size; Method: Linear gradient elution with 30% to 100% B in 7 min and then 30% B in 1 min and with a flow rate of 5.7 mL/min. Fraction collection was performed by split-flow MS detection.

Purity was determined by integration of the UV (254 nm) and ELSD traces. The retention times (RT) are expressed in minutes.

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument or at 400 MHz on a

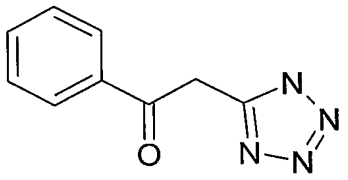
Bruker instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet, br s = broad singlet and br = broad signal.

For column chromatography silica gel of the type Kieselgel 60, 40-60 mesh ASTM (or Al_2O_3 (active, manufacturer: Qualigens India Ltd)) was used. Microwave heated experiments were performed with a Personal Chemistry Emrys Synthesiser or a Personal Chemistry Emrys Optimiser.

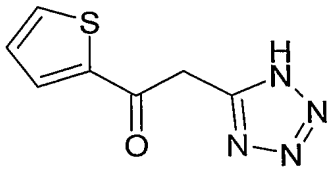
Examples

Preparation of intermediates

1-Phenyl-2-(2H-tetrazol-5-yl)-ethanone (intermediate for 5-(2-ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-ylamine):

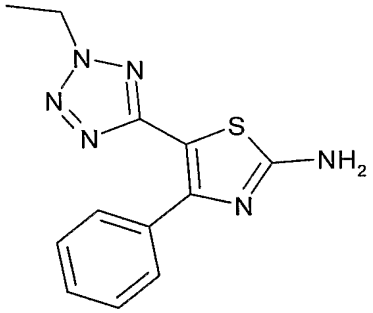


3-Oxo-3-phenyl-propionitrile (6.5 g, 45 mmol), sodium azide (3.3 g, 50 mmol) and triethylammonium chloride (6.7 g, 50 mmol) were stirred in dry toluene (100 mL) under argon at 90°C for 18h. A two-phase system was formed. The reaction mixture was cooled and extracted with NaOH (2M, 2x50 mL). The aqueous solution was poured into hydrochloric acid (4M, 200 mL) and the crude product precipitated and was filtered off and recrystalliced from acetonitrile. Yield: 74%.



2-(1H-Tetrazol-5-yl)-1-thiophen-2-yl-ethanone:

A mixture of 2-thenoylacetonitrile (9g, 59.3 mmol), Sodium azide (4.33g, 66.7 mmol) and triethylammoniumchloride (9.14g, 66.9 mmol) was stirred in dry toluene (139 mL) under argon atmosphere at 90°C for 18hrs. A two-phase system was formed, cooled and extracted with NaOH (2M, 3x500mL), and the aqueous solution was poured into hydrochloric acid (4M, 300mL) and the crude tetrazole was filtered off and recrystalised from acetonitrile. Yield: 43.5%.



5-(2-Ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-ylamine:

1-Phenyl-2-(2H-tetrazol-5-yl)-ethanone (3.3 g, 17.5 mmol), ethyl iodide (1.4 g, 17.5 mmol) and potassium carbonate (2.4 g, 17.5 mmol) was heated at reflux in acetone (50 mL) for 5 h under argon. The reaction mixture was then poured into water, made acidic with 6M HCl and extracted with diethyl ether. The organic extract was dried and evaporated to a red/orange oil. The oil was dissolved in diethyl ether (100 mL) and bromine (17.5 mmol) was added. The mixture was stirred over night at ambient temperature, then the solvent was removed in vacuo and the residue was redissolved in ethanol (100 mL). Thiourea (35 mmol) was added, and the resulting mixture was heated at reflux for 10 min., after which a solid precipitated. The reaction mixture was poured into water containing NaOH (17.5 mmol), and the orange crude product was recovered by filtration. The crude product was recrystallized from acetonitrile to give pale yellow solid. Yield: 0.6 g, 17%.

^{1}H NMR (d_6-DMSO) (250MHz): δ 7.65-7.61 (m, 2H), 7.54 (s br, 2H, NH2), 7.38-7.32 (m, 3H), 4.63 (q, 2H), 1.48 (t, 3H).

The following compounds were prepared analogously:

5-(2-Phenethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-ylamine:

^{1}H NMR (d_6-DMSO): δ 7.6-7.5 (m, 4H); 7.35-7.3 (m, 3H); 7.25 (t, 2H); 7.16 (m, 1H); 7.1 (d, 2H) 4.90 (t, 2H); 3.22 (t, 2H).

5-(2-Methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-ylamine:

^{1}H NMR (d_6-DMSO) (400Mhz): δ 7.62 (m, 2H); 7.54 (s, 2H); 7.36-7.33 (m, 3H); 4.29 (s, 3H).

4-Phenyl-5-(2-propyl-2H-tetrazol-5-yl)-thiazol-2-ylamine

^{1}H NMR ($CDCl_3$) (400Mhz): δ 7.70 (m, 2H); 7.40 (m, 3H); 6.20-5.80 (br, 2H) 4.51 (t, 2H); 2.01 (m, 2H); 0.96 (t, 3H).

5-(2-Butyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-ylamine

^{1}H NMR ($CDCl_3$) (400Mhz): δ 7.70 (m, 2H); 7.40 (m, 3H); 6.20-5.80 (br, 2H) 4.55 (t, 2H); 1.99-1.91 (m, 2H); 1.40-1.31 (m, 2H); 0.96 (t, 3H).

5-(2-Isobutyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-ylamine

^{1}H NMR (MeOD) (400Mhz): δ 7.57 (m, 2H); 7.36 (m, 3H); 4.41 (d, 2H); 2.26 (m, 1H); 0.93 (d, 6H).

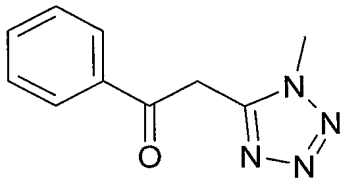
5-(2-Cyclopropylmethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-ylamine

^{1}H NMR (MeOD) (400Mhz): δ 7.61 (m, 2H); 7.37 (m, 3H); 4.45 (d, 2H); 1.37 (m, 1H); 0.67-0.62 (m, 2H); 0.48-0.44 (m, 2H).

5-(2-Methyl-2H-tetrazol-5-yl)-4-thiophen-2-yl-thiazol-2-ylamine:

Prepared from 2-(1H-tetrazol-5-yl)-1-thiophen-2-yl-ethanone and MeI and thiourea.

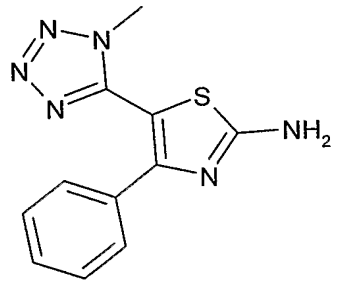
^{1}H NMR (d_6-DMSO) (400Mhz): δ 8.29 (d, 1H); 7.64 (s, 2H); 7.57 (d, 1H); 7.12 (t, 1H); 4.41 (s, 3H).



2-(1-Methyl-1H-tetrazol-5-yl)-1-phenyl-ethanone:

1-Phenyl-2-(2H-tetrazol-5-yl)-ethanone (13.24 g, 70.4 mmol) was dissolved in acetone (300 mL). MeI (4.6 mL, 73.9 mmol) and KCO_3 (10.68 g, 77.4 mmol) were added and the reaction mixture was heated to reflux for 30 min. The reaction mixture was filtered and the solvent was removed *in vacuo*. The crude product contains a mixture of 2-(1-methyl-1H-tetrazol-5-yl)-1-phenyl-ethanone and 2-(2-methyl-2H-tetrazol-5-yl)-1-phenyl-ethanone. The two compounds were separated by flash column chromatograpy using ethyl acetate/hexane (6/4) as eluent. 2-(1-Methyl-1H-tetrazol-5-yl)-1-phenyl-ethanone was obtained as a white solid. Yield: 34%.

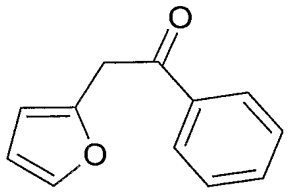
^{1}H NMR (d_6-DMSO) (500MHz): δ 8.09 (d, 2H), 7.73 (t, 1H), 7.60 (t, 2H), 5.05 (s, 2H), 4.00 (s, 3H).



5-(1-Methyl-1H-tetrazol-5-yl)-4-phenyl-thiazol-2-ylamine:

2-(1-Methyl-1H-tetrazol-5-yl)-1-phenyl-ethanone (4.9 g, 24.2 mmol) was dissolved in 1,2-dichloroethane (150 mL) and ether (100 mL). Brom (1.24 mL, 24.2 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. the solvent was removed *in vacuo.* The remenance was dissolved in ethanol (250 mL). Thiourea (3.67 g, 48.5 mmol) was added and the reaction mixture was heated at reflux for 20 min. The reaction mixture was poured into water/ice. Concentrated NaOH (aq) was added until pH = 10. The mixture was filtered and the solid product was recrystallised from ethylacetate/hexane. Yield: 58%.

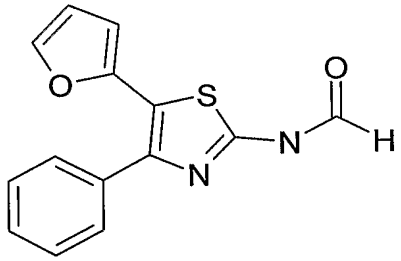
^{1}H NMR (d_6-DMSO) (500MHz): δ 7.7 (s, 2H), 7.35 (m, 3H), 7.25 (m, 2H), 3.5 (s, 3H).



2-Furan-2-yl-1-phenyl-ethanone (intermediate for 5-furan-2-yl-4-phenyl-thiazol-2-ylamine):

2-Furan-2-yl-3-oxo-3-phenyl-propionic acid ethyl ester, prepared as described by Dorsch J. B. and McElvain S. M., *J.Am.Chem.Soc* **1932**, *54*, 2960-2963; (10.0 g, 39 mmol) was dissolved in *N*-methylpyrolidin-2-one (13 mL) and acetic acid (3.9 mL) and lithium chloride (4.7g, 110 mmol) was added. The reaction mixture was heated at reflux for 7 h, then saturated aqueous $NaHCO_3$ was added and the mixture was extracted with diethyl ether. The organic extracts were dried over sodium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatograpy using 1% ethyl acetate in hexane as eluent. Yield: 6.2 g, 85%.

^{1}H NMR ($CDCl_3$) (400Mhz): δ 8.00 (m, 2H); 7.56 (m, 1H); 7.46 (m, 2H); 7.36 (m, 1H); 6.33 (q, 1H); 6.23 (q, 1H); 4.31 (s, 2H).

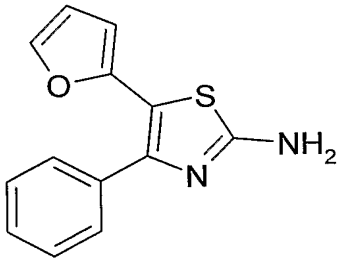


N-(5-Furan-2-yl-4-phenyl-thiazol-2-yl)-formamide (intermediate for 5-furan-2-yl-4-phenyl-thiazol-2-ylamine):

2-Furan-2-yl-1-phenyl-ethanone (14.0 g, 75 mmol) and thiourea (11.5 g, 150 mmol) was dissolved in DMF (30mL) and iodine (19.1 g, 75 mmol) was added. The reaction mixture was heated at 100 °C overnight, then diluted with water, made alkaline with saturated aqueous NH_4OH, and extracted with ether. The organic phases were washed

with water, dried over sodium sulfate, filtered, concentrated and purified by flash column chromatograpy using 1% ethyl acetate in hexane as eluent. Yield: 9.2 g, 45%

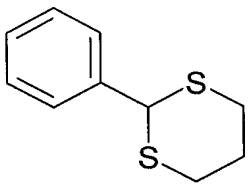
^{1}H NMR ($CDCl_3$) (400MHz): δ 7.57 (m, 2H); 7.50 (m, 3H); 7.44 (s, 1H); 7.38 (m, 1H); 6.28 (m, 1H); 6.20 (s, 1H).



5-Furan-2-yl-4-phenyl-thiazol-2-ylamine:

N-(5-Furan-2-yl-4-phenyl-thiazol-2-yl)-formamide (3.9 g, 14.5 mmol) was dissolved in a mixture of methanol (45 mL) and THF (62 mL), and added dropwise HCl (conc.) (6 mL). The reaction mixture was stirred over night and the solvent was evaporated. The residue was extracted with ethyl acetate, and washed with $NaHCO_3$ (aq.; sat.), then washed with water, dried over sodium sulfate and concentrated in vacuo. The crude product was purified on neutral Al_2O_3 using 30-35% ethyl acetate in hexane as eluent. Yield: 2.6 g, 76%.

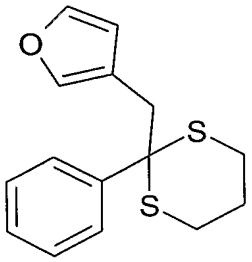
^{1}H NMR ($CDCl_3$) (400MHz): δ 7.54 (m, 2H); 7.33 (m, 4H); 6.32 (q, 1H); 6.17 (q, 1H); 5.45 (br s, 2H).



2-Phenyl-[1,3]dithiane (intermediate for 5-furan-3-yl-4-phenyl-thiazol-2-ylamine):

To a solution of benzaldehyde (15.0 g, 141 mmol) in chloroform (150 mL), propane-1,3-dithiol (16.9 g, 155 mmol) and boron trifluoride etherate (26.1 g, 183 mmol) were added. The reaction mixture was stirred at ambient temperature for 24 h, and was then poured into ice-cold aqueous sodium hydroxide (10%) and extracted with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, concentrated and purified by flash column chromatograpy using 1% ethyl acetate in hexane as eluent. Yield: 21.2 g, 77%.

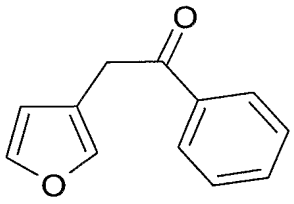
^{1}H NMR ($CDCl_3$) (400MHz): δ 7.46 (m, 2H); 7.30 (m, 3H); 5.16 (s, 1H); 3.06 (m, 2H); 2.90 (m, 2H); 2.17 (m, 1H); 1.93 (m, 1H).



3-(2-Phenyl-[1,3]dithian-2-ylmethyl)-furan (intermediate for 5-furan-3-yl-4-phenyl-thiazol-2-ylamine):

A stirred suspension of sodium *tert*-butoxide (5.16 g, 54 mmol) in dry hexane (120 mL) was added n-butyl lithium (34 mL, 51 mmol) at 0 °C and stirred for 1 h at 0°C, and then for 1 h at room temperature. The mixture was cooled to –78 °C, and transferred to a preformed mixture of 2-phenyl-[1,3]dithiane (10.0 g, 51 mmol) dissolved in dry THF (120 mL) at –78 °C, and n-butyl lithium (34 mL, 51 mmol) and kept for 15 min. A dark brown colored solution was observed. After stirring for 1 h at –78 °C, 3-bromomethyl-furan (Danso-Danquah R.E. and Scott A. I. *Tetrahedron*, **1993**, *49*, 8195-8210; New D. G. et al, *J.Org.Chem.*, **1996**, *61*, 1578-1598) (10.7 g, 66 mmol) was added *via* canula. After 30 min., the reaction mixture was quenched with water and warmed to ambient temperature. The reaction mixture was extracted with diethyl ether, and the organic extracts were dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatograpy using 0.2-0.5% ethyl acetate in hexane as eluent. Yield: 5.6 g, 32%.

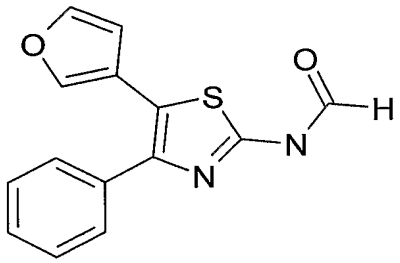
^{1}H NMR ($CDCl_3$) (400MHz): δ 7.79 (m, 2H); 7.33 (m, 2H); 7.26 (m, 1H); 7.17 (m, 1H); 6.92 (m, 1H); 5.73 (s, 1H); 3.11 (s, 2H); 2.68 (m, 4H); 1.93 (m, 2H).



2-Furan-3-yl-1-phenyl-ethanone (intermediate for 5-furan-3-yl-4-phenyl-thiazol-2-ylamine):

3-(2-Phenyl-[1,3]dithian-2-ylmethyl)-furan (11.5 g, 41 mmol) was suspended in 9:1 methanol/water (v/v) (150 mL) with slight heating. A solution of $HgCl_2$ (22.3 g, 82 mmol) in methanol/water (50 mL) and solid HgO (8.0 g, 36.9 mmol) was added, and the mixture was heated at reflux under a nitrogen atmosphere for 6-7 h. The reaction mixture was filtered through celite to remove solids, and then concentrated. The resulting aqueous mixture was extracted with ethyl acetate, the combined organic extracts were washed with water, dried over sodium sulfate, and evaporated. The crude product was purified by flash column chromatograpy using 2% ethyl acetate in hexane as eluent. Yield: 5.7 g, 75%.

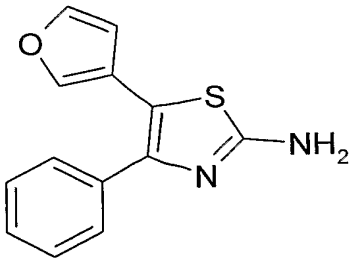
^{1}H NMR ($CDCl_3$) (400MHz): δ 8.00 (m, 2H); 7.57 (s, 1H); 7.47 (m, 2H); 7.39 (m, 2H); 6.36 (s, 1H); 4.11 (s, 2H).



N-(5-Furan-3-yl-4-phenyl-thiazol-2-yl)-formamide (intermediate for 5-furan-3-yl-4-phenyl-thiazol-2-ylamine):

To a solution of 2-furan-3-yl-1-phenyl-ethanone (5.7 g, 31 mmol) and thiourea (4.7 g, 61 mmol) in DMF (57 mL) was and added iodine (7.8 g, 31 mmol). The reaction mixture was heated at 100 °C overnight, then it was diluted with water and made alkaline with saturated aqueous NH_4OH, and extracted with ether. The organic phases were washed with water, dried over sodium sulfate, concentrated and purified on neutral Al_2O_3 using 50% ethyl acetate in hexane as eluent. Yield: 5.7 g, 69%.

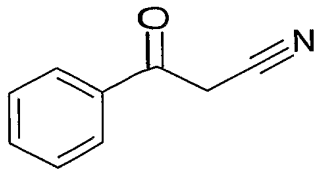
GC-MS (M^+) 270



5-Furan-3-yl-4-phenyl-thiazol-2-ylamine:

N-(5-Furan-3-yl-4-phenyl-thiazol-2-yl)-formamide (5.7 g, 21 mmol) was dissolved in a mixture of methanol (210 mL) and THF (90 mL), and conc. squeous hydrochloric acid (8.7 mL) was added dropwise at room temperature. The reaction mixture was stirred over night and the solvent was removed by evaporation. The residue was extracted with ethyl acetate, and washed with $NaHCO_3$ (aq.; sat.) and water and dried over sodium sulfate. The solvent was removed and the crude product was purified on neutral Al_2O_3 using 30-35% ethyl acetate in hexane as eluent. Yield: 2.5 g, 49%.

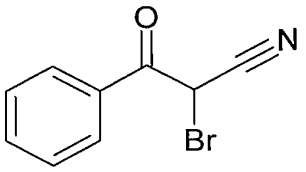
^1H NMR ($CDCl_3$) (400MHz): δ 7.53 (m, 2H); 7.38 (q, 1H); 7.31 (m, 4H); 6.19 (m, 1H); 5.26 (br s, 2H).



3-Oxo-3-phenylpropionitril (intermediate for 5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-ylamine):

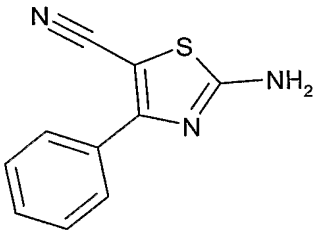
Ethyl benzoate (20 g, 133 mmol) and NaOMe (133 mmol, from 3 g Na) in methanol was mixed and heated with stirring to 80 °C until a homogeneous gelatinous mass had formed. Acetonitrile (6.8 g, 165 mmol) was then added slowly under the surface of this mass over a period of 30 min. The temperature was raised to 120 °C and heated at reflux for 24h, and the reaction mixture was then cooled on an ice bath and treated with water and diethyl ether until the solid material had dissolved. The aqueous layer was separated and acidified with 5% H_2SO_4, washed with $NaHCO_3$ (aq,; sat.), dried over sodium sulfate and concentrated. The crude product was used in the next reaction without any further purification. Yield: 7.3 g, 37.8 %.

^1H NMR ($CDCl_3$) (400MHz): δ 7.91 (m, 2H); 7.66 (m, 1H); 7.51 (m, 2H); 4.08 (s, 2H).



2-Bromo-3-oxo-3-phenylpropionitril (intermediate for 5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-ylamine):

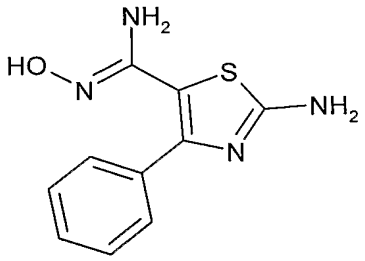
3-Oxo-3-phenylpropionitril (1.5 g, 10 mmol) was dissolved in dry chloroform (10 mL) at 0 °C, and pyridine (0.81 mL, 10 mmol) was added. Bromine (4.7 mL, 10 mmol) dissolved in chloroform (4.7 mL) was added dropwise over an hour, then the reaction mixture was heated at 45°C over night. The reaction mixture was diluted with chloroform and washed with water. The organic phases were dried over sodium sulfate and evaporated to give the crude product, which was used in the next reaction without any further purification.



2-Amino-4-phenyl-thiazole-5-carbonitrile (intermediate for 5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-ylamine):

2-Bromo-3-oxo-3-phenylpropionitrile (0.5 g, 3.4 mmol) was mixed with thiourea (0.52 g, 6.8 mmol) and iodine (0.43 g, 3.4 mmol) and the mixture was heated on a steam bath for 12 h. It was then diluted with water and made alkaline with saturated aqueous NH_4OH, and extracted with ethyl acetate. The organic phases were washed with water and brine, dried over sodium sulfate, and evaporated to dryness to give the crude product, which was used in the next reaction without any further purification. Yield: 0.2 g, 29 %.

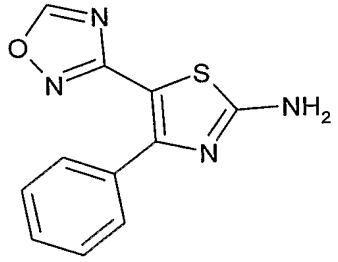
^1H NMR (d_6-DMSO) (400MHz): δ 8.26 (s, 2H); 7.91 (m, 2H); 7.50 (m, 3H).



2-Amino-N-hydroxy-4-phenyl-thiazole-5-carboxamidine (intermediate for 5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-ylamine):

2-Amino-4-phenyl-thiazole-5-carbonitrile (0.13g, 0.6 mmol) was suspended in 1:1 water/ethanol (v/v) (24 mL) and added hydroxylamine hydrochloride (1.47 g, 21 mmol) and potassium carbonate (1.86 g, 13 mmol). The reaction mixture was heated at reflux for 3 days, then the solvent was reduced and the aqueous phase was extracted with dichloromethane. The organic layer was washed with water and brine, and was dried over sodium sulfate. The solvent was evaporated to yield a yellow solid. Yield: 0.1g, 66%.

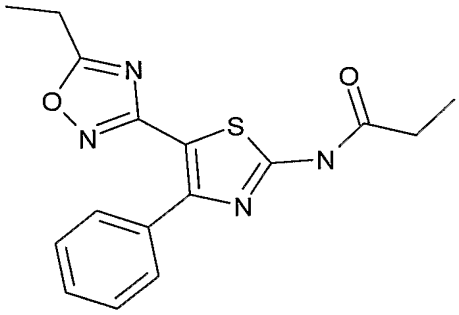
^{1}H NMR (D_6-DMSO) (400MHz): δ 9.52 (s, 1H); 7.64 (m, 2H); 7.31 (m, 3H); 7.14 (s, 2H); 5.50 (s, 2H).



5-[1,2,4]Oxadiazol-3-yl-4-phenyl-thiazol-2-ylamine:

2-Amino-*N*-hydroxy-4-phenyl-thiazole-5-carboxamidine (1.0 g, 4.3 mmol) was dissolved in methanol (20 mL), and trimethyl orthoformate (1.2 mL, 11 mmol) containing boron trifluoride etherate (0.2 mL, 1.6 mmol) was added and the mixture was heated at reflux for 3 h. The reaction mixture was cooled, and the solvent was removed under reduced pressure at 20°C. The residue was extracted with ethyl acetate, and the solution was washed with saturated aqueous $NaHCO_3$ dried over sodium sulfate and evaporated. The crude product was purified by flash column chromatograpy, eluted with the gradient of 10-18% ethyl acetate in hexanes to get the product (the product was eluted by 18% ethyl acetate in hexanes). Yield: 0.1 g, 10%

^{1}H NMR (d_6-DMSO) (400MHz): δ 9.47 (s, 1H); 7.72 (s, 2H); 7.63 (m, 2H); 7.38 (m, 3H).



N-[5-(5-Ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-propionamide:

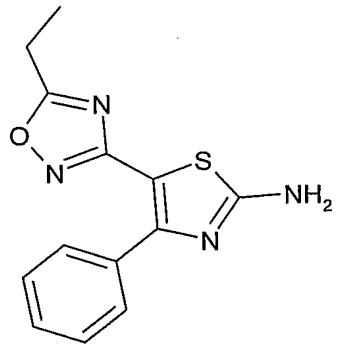
2-Amino-*N*-hydroxy-4-phenyl-thiazole-5-carboxamidine (1.5 g, 6.4 mmol) was dissolved in dry THF (50 mL). Ethyl-diisopropyl-amine (2.5 mL) and propionylchloride (2.8 mL, 5eq) was added. The reaction mixture was stirred overnight at room temperature. pH was adjusted to pH ~2 by addition of HCl in ethanol. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated to yield a yellow oil. The crude product was purified by flash column chromatograpy, eluted with 30% ethyl acetate in hexanes to give the product as a white solid. Yield: 49%.

The following compound was prepared analogously:

N-[5-(5-Methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide

Prepared from 2-amino-*N*-hydroxy-4-phenyl-thiazole-5-carboxamidine acetyl chloride.

^{1}H NMR ($CDCl_3$) (500MHz): δ 11.55 (s, 1H); 7.75 (m, 2H); 7.43 (m, 3H); 2.59 (s, 3H); 1.5 (s, 3H).



5-(5-Ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine:

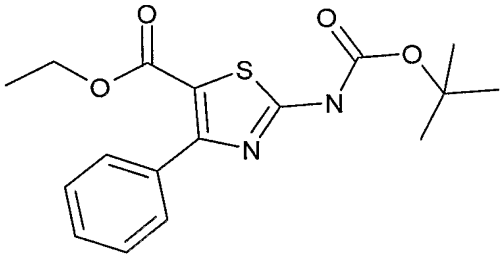
N-[5-(5-Ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-propionamide (1.02 g, 3.1 mmol) was suspended in MeOH (40 mL), konc. HCl(aq) was added and the reaction mixture was heated at refluc for 2 h. Saturated aqueous $NaHCO_3$ (100 mL) was added to the reaction mixture. The aqueous phase was extracted with ethyl acetate (2 x 75 mL). The organic phase was dried with $MgSO_4$ and the solvent was evaporated to yield white solid. Yield: 91%.

The following compound was prepared analogously:

5-(5-Methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine

Prepared from *N*-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide.

^1H NMR ($CDCl_3$) (500MHz): δ 7.7 (m, 2H); 7.4 (m, 3H); 5.3 (s, 2H); 2.55 (s, 3H).



2-tert-Butoxycarbonylamino-4-phenyl-thiazole-5-carboxylic acid ethyl ester

2-Amino-4-phenyl-thiazole-5-carboxylic acid ethyl ester (2 g, 8.1 mmol), was dissolved in THF (50mL). Triethylamine (25mL), dimethyl-pyridin-4-yl-amine (0.1 g, 0.8 mmol) and ditert-butil-dicarbonate (2 g, 9.2 mmol) were added. The reaction mixture was stirred overnight. The reaction mixture was filtered and solvents were removed *in vacuo*. The crude product was purified by flash column chromatograpy, eluted with the gradient of 0-10% ethyl acetate in hexanes to give the product as a white solid. Yield: 53%.

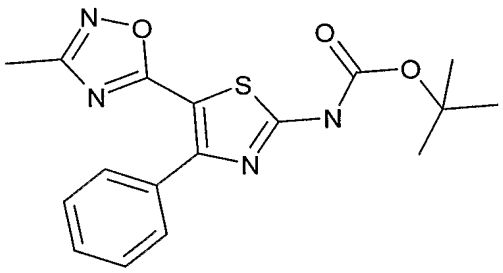
N-*hydroxy-propionamidine*

Hydroxyl ammonium chloride (69.5 ml, 1 mol) was dissolved in ethanol. NaOH (Aq, 28%, 110 mL) and propionitrile (71 mL, 1 mol) were added. The reaction mixture was stirred at 40°C for 48 h. The reaction mixture was filtered. The solvent was removed from the filtrate by evaporation *in vacuo*. The crude product was purified by flash column chromatograpy, eluted with the gradient of ethyl acetate/ethanol 9/1 to give the product. Yield: 52%.

The following compound was prepared analogously:

N-hydroxy-acetamidine

Prepared from acetonitrile.



[5-(3-Methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-carbamic acid tert-butyl ester:

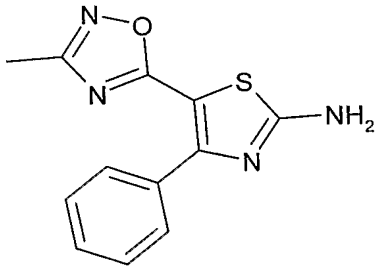
2-Tert-butoxycarbonylamino-4-phenyl-thiazole-5-carboxylic acid ethyl ester (1.9 g 5.6 mmol) was dissolved in dry THF (60 mL). Sodium hydride (60% in oil) and *N*-hydroxy-acetamidine (0.83g, 11.2 mmol) dissolved in THF (30 mL) was added. The reaction mixture was heated to reflux over night. The reaction mixture was cooled and ethyl acetate (75 mL) glacial aceticacid (0.43 g) were added. The organic mixture was washed with brine (75 mL). The aqueous phase was extracted with ethylacetate The combined organic phases was washed with brine (50 mL) dried with $MgSO_4$ and solvents were removed *in vacuo* to give a solid. Yield: 36%.

^1H NMR ($CDCl_3$) (500MHz): δ 8.55 (br, 1H); 7.72 (m, 2H); 7.43 (m, 3H); 2.4 (s, 3H); 1.5 (s, 9H).

The following compound was prepared analogously:

[5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-carbamic acid tert-butyl ester:

Prepared from 2-tert-butoxycarbonylamino-4-phenyl-thiazole-5-carboxylic acid ethyl ester and *N*-hydroxy-propionamidine.



5-(3-Methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine:

[5-(3-Methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-carbamic acid tert-butyl ester was suspended in glacial acetic acid (20 mL). TFA (20 mL) was added. The reactionmixture was stirred at room temperature overnight. The reaction mixture was added to brine (100 mL) and pH was adjusted to pH ~10 with ammonia. The mixture was extracted with EtOAc (2 x 75 mL). The combined organic phases was washed with brine (50 mL), dried with $MgSO_4$ and solvents were removed *in vacuo* to give a white solid. Yield 98%.

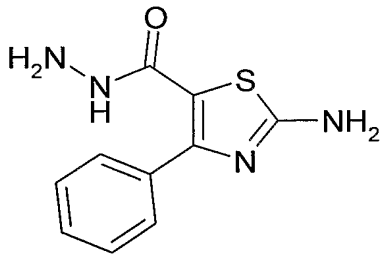
^{1}H NMR (d_6-DMSO) (500MHz): δ 8.03 (br, 2H); 7.64 (m, 2H); 7.43 (m, 3H); 2.25 (s, 3H).

The following compound was prepared analogously:

5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine:

Prepared from [5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-carbamic acid tert-butyl ester.

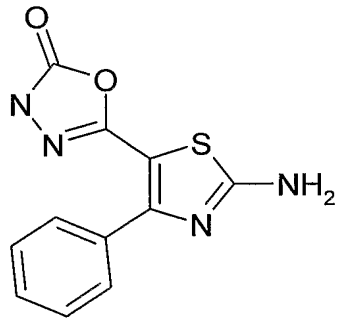
^{1}H NMR (d_6-DMSO) (500MHz): δ 8.03 (br, 2H); 7.64 (m, 2H); 7.43 (m, 3H); 2.67 (q, 2H); 1.18 (t, 3H).



2-Amino-4-phenyl-thiazole-5-carboxylic acid hydrazide:

2-Amino-4-phenyl-thiazole-5-carboxylic acid ethyl ester (5.0 g, 20 mmol) was suspended in methanol. Hydrazine monohydrate (5 mL, 100 mmol) was added and heated to reflux for 2 h. Hydrazine monohydrate (10 mL) was added and heated to reflux for 48 h. Water (100mL) was added to the reaction mixture and the methanol was removed by evaporation *in vacuo.* The product precipitates and the solid product is collected by filtration. Yield: 70%.

^{1}H NMR (d_6-DMSO) (500MHz): δ 8.9 (s, 1H); 7.6 (m, 2H); 7.3 (m, 5H); 4.35 (s, 2H).



5-(2-Amino-4-phenyl-thiazol-5-yl)-3H-[1,3,4]oxadiazol-2-one:

2-Amino-4-phenyl-thiazole-5-carboxylic acid hydrazide (1 g, 4.3 mmol) was suspended in tetrahydrofurane (50 mL). Triethylamine (5 mL, 40 mmol) and carbonyldiimidazole (0.83, 5.1 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo*. The crude product was purified by flash column chromatograpy, eluted with the ethyl acetate/hexanes (1/1) to give the product as a solid. Yield: 20%.

(3,4-Dimethoxy-phenyl)-acetyl chloride:

(3,4-Dimethoxy-phenyl)-acetic acid was dissolved in 1,2-dichloroethant (7 mL) and DMF (0.07 nL). Oxalylchloride was added dropwise and the reaction mixture was

stirred under argon for 1 h at room temperature. The solvent was removed *in vacuo*. The crude product was used without further purification.

Preparation of the compounds of the invention

1: *2-(3,4-Dimethoxy-phenyl)-N-[5-(2-ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide*

200 µL of a 0.6M stock solution of (3,4-dimethoxy-phenyl)-acetic acid was mixed with 200 µL of a 0.3M stock solution of EDC containing 1 eq. of ethyl-diisopropyl-amine. Then 100 µL of a 0.3M stock solution of 5-(2-ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-ylamine containing 1 eq. of DMAP was added. The reaction mixture was shaken overnight at ambient temperature. Purification was performed by preparative LC-MS. Yield: 13%.

LC/MS (m/z) 452.0 (MH+); RT = 2.82; purity (UV, ELSD): 97%; 100%.

The following compounds were prepared analogously:

2: *2-(3,4-Dimethoxy-phenyl)-N-(5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-acetamide*

LC/MS (m/z) 422.9 (MH+); RT = 2.75; purity (UV, ELSD): 98%; 99%.

3: *N-(5-Furan-3-yl-4-phenyl-thiazol-2-yl)-isobutyramide*

LC/MS (m/z) 313.1 (MH+); RT = 3.15; purity (UV, ELSD): 92%; 99%.

4: *Cyclopropanecarboxylic acid [5-(2-ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*

LC/MS (m/z) 341.1 (MH+); RT = 2.70; purity (UV, ELSD): 98%; 100%.

5: *Furan-3-carboxylic acid [5-(2-ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*

LC/MS (m/z) 367.1 (MH+); RT = 2.89; purity (UV, ELSD): 72%; 92%.

6: *N-[5-(2-Ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide*

LC/MS (m/z) 343.0 (MH+); RT = 2.81; purity (UV, ELSD): 98%; 99%.

7: *Furan-2-carboxylic acid [5-(2-ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
LC/MS (m/z) 367.2 (MH+); RT = 2.79; purity (UV, ELSD): 97%; 99%.

8: *Cyclohexanecarboxylic acid [5-(2-ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
LC/MS (m/z) 383.2 (MH+); RT = 3.31; purity (UV, ELSD): 93%; 99%.

9: *2-Cyclopentyl-N-[5-(2-ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide*
LC/MS (m/z) 383.2 (MH+); RT = 3.34; purity (UV, ELSD): 99%; 100%.

10: *N-[5-(2-Ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide*
LC/MS (m/z) 329.1 (MH+); RT = 2.63; purity (UV, ELSD): 99%; 100%.

11: *Cyclopropanecarboxylic acid (5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-amide*
LC/MS (m/z) 312.9 (MH+); RT = 2.55; purity (UV, ELSD): 95%; 100%.

12: *Thiophene-3-carboxylic acid [5-(2-ethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
LC/MS (m/z) 383.1 (MH+); RT = 3.03; purity (UV, ELSD): 90%; 99%.

13: *2-Cyclopentyl-N-(5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-acetamide*
LC/MS (m/z) 355.1 (MH+); RT = 3.18; purity (UV, ELSD): 97%; 99%.

14: *Furan-3-carboxylic acid [5-(2-phenethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
LC/MS (m/z) 443.0 (MH+); RT = 3.38; purity (UV, ELSD): 70%; 93%.

15: *N-(5-Furan-2-yl-4-phenyl-thiazol-2-yl)-isobutyramide*
LC/MS (m/z) 313.1 (MH+); RT = 3.12; purity (UV, ELSD): 98%; 97%.

16: *Furan-2-carboxylic acid (5-furan-3-yl-4-phenyl-thiazol-2-yl)-amide*

LC/MS (m/z) 337.0 (MH+); RT = 3.14; purity (UV, ELSD): 96%; 99%.

17: *2-(3,4-Dimethoxy-phenyl)-N-(5-furan-2-yl-4-phenyl-thiazol-2-yl)-acetamide*
LC/MS (m/z) 421.1 (MH+); RT = 3.02; purity (UV, ELSD): 98%; 98%.

18: *Cyclopropanecarboxylic acid (5-furan-3-yl-4-phenyl-thiazol-2-yl)-amide*
100 µL of a 0.3M stock solution of 5-furan-3-yl-4-phenyl-thiazol-2-ylamine and 120 µL of a 0.3M stock solution of pyridine were mixed with 120 µL of a 0.3M stock solution of cyclopropanecarbonyl chloride. The reaction mixture was shaken overnight at ambient temperature. Purification was performed by preparative LC-MS. Yield: 1.1 mg (12)%.
LC/MS (m/z) 311.1 (MH+); RT = 3.11; purity (UV, ELSD): 80%; 97%.

The following compounds were prepared analogously:

19: *2-(3-Methoxy-phenyl)-N-(5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-acetamide*
LC/MS (m/z) 393.1 (MH+); RT = 2.95; purity (UV, ELSD): 96%; 100%.

20: *2-(3-Methoxy-phenyl)-N-[5-(2-phenethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide*
LC/MS (m/z) 497.1 (MH+); RT = 3.58; purity (UV, ELSD): 77%; 99%.

21: *N-(5-Furan-2-yl-4-phenyl-thiazol-2-yl)-2,2-dimethyl-propionamide*
LC/MS (m/z) 327.2 (MH+); RT = 3.48; purity (UV, ELSD): 77%; 99%.

22: *N-(5-Furan-3-yl-4-phenyl-thiazol-2-yl)-propionamide*
LC/MS (m/z) 299.1 (MH+); RT = 2.95; purity (UV, ELSD): 96%; 99%.

23: *N-[5-(2-Phenethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide*
LC/MS (m/z) 419.3 (MH+); RT = 3.33; purity (UV, ELSD): 97%; 99%.

24: *N-(5-Furan-2-yl-4-phenyl-thiazol-2-yl)-propionamide*
LC/MS (m/z) 299.1 (MH+); RT = 2.99; purity (UV, ELSD): 99%; 99%.

25: *Furan-2-carboxylic acid [5-(2-methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
LC/MS (m/z) 353.1 (MH+); RT = 2.62; purity (UV, ELSD): 96%; 99%.

26: *3,3-Dimethyl-N-[5-(2-methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-butyramide*
LC/MS (m/z) 357.1 (MH+); RT = 3.06; purity (UV, ELSD): 98%; 99%.

27: *Cyclopropanecarboxylic acid [5-(2-methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
LC/MS (m/z) 327.2 (MH+); RT = 2.49; purity (UV, ELSD): 77%; 95%.

28: *2-Cyclopentyl-N-[5-(2-methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide*
LC/MS (m/z) 369.1 (MH+); RT = 3.13; purity (UV, ELSD): 94%; 99%.

29: *N-[5-(2-Methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide*
LC/MS (m/z) 329.1 (MH+); RT = 2.63; purity (UV, ELSD): 96%; 99%.

30: *3-Methyl-N-[5-(2-methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-butyramide*
LC/MS (m/z) 343.1 (MH+); RT = 2.86; purity (UV, ELSD): 96%; 99%.

31: *N-[5-(2-Methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide*
LC/MS (m/z) 315.0 (MH+); RT = 2.40; purity (UV, ELSD): 90%; 99%.

32: *N-[5-(2-Methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide*
LC/MS (m/z) 377.1 (MH+); RT = 2.85; purity (UV, ELSD): 90%; 99%.

33: *Hexanoic acid [5-(2-methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*

LC/MS (m/z) 357.1 (MH+); RT = 3.13; purity (UV, ELSD): 99%; 99%.

34: *N-[5-(2-Methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide*

LC/MS (m/z) 383.1 (MH+); RT = 2.83; purity (UV, ELSD): 80%; 95%.

35: *N-[5-(2-Methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide*

LC/MS (m/z) 301.0 (MH+); RT = 2.13; purity (UV, ELSD): 94%; 99%.

36: *2,2-Dimethyl-N-[5-(2-methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide*

LC/MS (m/z) 343.1 (MH+); RT = 2.92; purity (UV, ELSD): 95%; 99%.

37: *Thiophene-3-carboxylic acid [5-(2-methyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]- amide*

LC/MS (m/z) 369.1 (MH+); RT = 2.85; purity (UV, ELSD): 85%; 99%.

38: *N-[4-Phenyl-5-(2-propyl-2H-tetrazol-5-yl)-thiazol-2-yl]-isobutyramide*

LC/MS (m/z) 357.1 (MH+); RT = 3.08; purity (UV, ELSD): 99%; 99%.

39: *3-Methyl-N-[4-phenyl-5-(2-propyl-2H-tetrazol-5-yl)-thiazol-2-yl]-butyramide*

LC/MS (m/z) 371.2 (MH+); RT = 3.28; purity (UV, ELSD): 97%; 99%.

40: *N-[4-Phenyl-5-(2-propyl-2H-tetrazol-5-yl)-thiazol-2-yl]-propionamide*

LC/MS (m/z) 343.1 (MH+); RT = 2.87; purity (UV, ELSD): 90%; 97%.

41: *2-Phenyl-N-[4-phenyl-5-(2-propyl-2H-tetrazol-5-yl)-thiazol-2-yl]-acetamide*

LC/MS (m/z) 405.1 (MH+); RT = 3.29; purity (UV, ELSD): 94%; 99%.

42: *N-[4-Phenyl-5-(2-propyl-2H-tetrazol-5-yl)-thiazol-2-yl]-2-thiophen-2-yl-acetamide*

LC/MS (m/z) 411.1 (MH+); RT = 3.22; purity (UV, ELSD): 88%; 97%.

43: *N-[4-Phenyl-5-(2-propyl-2H-tetrazol-5-yl)-thiazol-2-yl]-acetamide*
LC/MS (m/z) 329.1 (MH+); RT = 2.65; purity (UV, ELSD): 98%; 99%.

44: *2,2-Dimethyl-N-[4-phenyl-5-(2-propyl-2H-tetrazol-5-yl)-thiazol-2-yl]-propionamide*
LC/MS (m/z) 371.2 (MH+); RT = 3.34; purity (UV, ELSD): 95%; 99%.

45: *Thiophene-3-carboxylic acid [4-phenyl-5-(2-propyl-2H-tetrazol-5-yl)-thiazol-2-yl]-amide*
LC/MS (m/z) 397.1 (MH+); RT = 3.29; purity (UV, ELSD): 93%; 99%.

46: *N-[5-(2-Butyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide*
LC/MS (m/z) 371.2 (MH+); RT = 3.31; purity (UV, ELSD): 97%; 99%.

47: *2-Cyclopentyl-N-[5-(2-isobutyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide*
LC/MS (m/z) 411.2 (MH+); RT = 3.73; purity (UV, ELSD): 98%; 99%.

48: *N-[5-(2-Isobutyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide*
LC/MS (m/z) 425.1 (MH+); RT = 3.40; purity (UV, ELSD): 84%; 95%.

49: *N-[5-(2-Cyclopropylmethyl-2H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-3-methyl-butyramide*
LC/MS (m/z) 383.2 (MH+); RT = 3.32; purity (UV, ELSD): 86%; 98%.

50: *Furan-2-carboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and furan-2-carbonyl chloride.
LC/MS (m/z) 353.4 (MH+); RT = 2.84

51: *3,3-Dimethyl-N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-butyramide*

Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and 3,3-dimethyl-butyryl chloride.

LC/MS (m/z) 357.4 (MH+); RT = 3.21

52: *N-[5-(3-Methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-benzamide*

Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and benzoyl chloride.

LC/MS (m/z) 363.4 (MH+); RT = 3.22

53: *N-[5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-benzamide*

Prepared from 5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and benzoyl chloride.

LC/MS (m/z) 377.4 (MH+); RT = 3.48

54: *N-[5-(5-Methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-benzamide*

Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and benzoyl chloride.

LC/MS (m/z) 363.4 (MH+); RT = 3.11

55: *Cyclopropanecarboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*

Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and cyclopropanecarbonyl chloride.

LC/MS (m/z) 327.4 (MH+); RT = 2.74

56: *Cyclopropanecarboxylic acid [5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*

Prepared from 5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and cyclopropanecarbonyl chloride.

LC/MS (m/z) 341.4 (MH+); RT = 3.05

57: *Cyclopropanecarboxylic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide*

Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and cyclopropanecarbonyl chloride.

LC/MS (m/z) 327.4 (MH+); RT = 2.62

58: *Cyclopropanecarboxylic acid [5-(5-ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide*

Prepared from 5-Ethyl-3-(4-phenyl-thiazol-5-yl)-[1,2,4]oxadiazole and cyclopropanecarbonyl chloride.

LC/MS (m/z) 341.4 (MH+); RT = 2.96

59: *2-Cyclopentyl-N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide*

Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and cyclopentyl-acetyl chloride.

LC/MS (m/z) 369.5 (MH+); RT = 3.43

60: *2-Cyclopentyl-N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide*

Prepared from 5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and cyclopentyl-acetyl chloride.

LC/MS (m/z) 383.5 (MH+); RT = 3.68

61: *2-Cyclopentyl-N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide*

Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and cyclopentyl-acetyl chloride.

LC/MS (m/z) 369.5 (MH+); RT = 3.30

62: *2-Cyclopentyl-N-[5-(5-ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide*

Prepared from 5-ethyl-3-(4-phenyl-thiazol-5-yl)-[1,2,4]oxadiazole and cyclopentyl-

acetyl chloride.
LC/MS (m/z) 383.5 (MH+); RT = 3.57

63: *Cyclohexanecarboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and cyclohexanecarbonyl chloride.
LC/MS (m/z) 369.5 (MH+); RT = 3.41

64: *Cyclohexanecarboxylic acid [5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
Prepared from 5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and cyclohexanecarbonyl chloride.
LC/MS (m/z) 383.5 (MH+); RT = 3.67

65: *Cyclohexanecarboxylic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide*
Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and cyclohexanecarbonyl chloride.
LC/MS (m/z) 369.5 (MH+); RT = 3.29

66: *N-[5-(1-Methyl-1H-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide*
Prepared from 5-(1-methyl-1H-tetrazol-5-yl)-4-phenyl-thiazol-2-ylamine and isobutyryl chloride.
LC/MS (m/z) 329.4 (MH+); RT = 2.48

67: *N-[5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide*
Prepared from 5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and isobutyryl chloride.
LC/MS (m/z) 343.4 (MH+); RT = 3.17

68: *3-Methyl-N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-butyramide*

Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and 3-methyl-butyryl chloride.

LC/MS (m/z) 343.4 (MH+); RT = 3.13

69: *N-[5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-3-methyl-butyramide*

Prepared from 5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and 3-methyl-butyryl chloride.

LC/MS (m/z) 357.4 (MH+); RT = 3.40

70: *3-Methyl-N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-butyramide*

Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and 3-methyl-butyryl chloride.

LC/MS (m/z) 343.4 (MH+); RT = 3.00

71: *N-[5-(3-Methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide*

Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and propionyl chloride.

LC/MS (m/z) 315.4 (MH+); RT = 2.63

72: *N-[5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide*

Prepared from 5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and propionyl chloride.

LC/MS (m/z) 329.4 (MH+); RT = 2.94

73: *N-[5-(5-Methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-propionamide*

Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and propionyl chloride.

LC/MS (m/z) 315.4 (MH+); RT = 2.52

74: *N-[5-(3-Methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide*

Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and

phenyl-acetyl chloride.
LC/MS (m/z) 377.4 (MH+); RT = 3.15

75: *N-[5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide*
Prepared from 5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and phenyl-acetyl chloride.
LC/MS (m/z) 391.5 (MH+); RT = 3.39

76: *N-[5-(5-Methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide*
Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and phenyl-acetyl chloride.
LC/MS (m/z) 377.4 (MH+); RT = 3.04

77: *N-[5-(5-Oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide*
Prepared from 5-(2-amino-4-phenyl-thiazol-5-yl)-3H-[1,3,4]oxadiazol-2-one and phenyl-acetyl chloride.
LC/MS (m/z) 379.4 (MH+); RT = 2.59

78: *N-[5-(5-Ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-3-phenyl-acrylamide*
Prepared from 5-ethyl-3-(4-phenyl-thiazol-5-yl)-[1,2,4]oxadiazole and 3-phenyl-acryloyl chloride.
LC/MS (m/z) 403.5 (MH+); RT = 3.54

79: *Hexanoic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and hexanoyl chloride.
LC/MS (m/z) 357.4 (MH+); RT = 3.41

80: *Hexanoic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide*
Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and hexanoyl chloride.
LC/MS (m/z) 357.4 (MH+); RT = 3.29

81: *N-[5-(3-Methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide*

Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and thiophen-2-yl-acetyl chloride.

LC/MS (m/z) 383.5 (MH+); RT = 3.06

82: *N-[5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide*

Prepared from 5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and thiophen-2-yl-acetyl chloride.

LC/MS (m/z) 397.5 (MH+); RT = 3.31

83: *N-[5-(5-Methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide*

Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and thiophen-2-yl-acetyl chloride.

LC/MS (m/z) 383.5 (MH+); RT = 2.97

84: *N-[5-(3-Methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide*

Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and acetyl chloride.

LC/MS (m/z) 301.3 (MH+); RT = 2.38

85: *N-[5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide*

Prepared from 5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and acetyl chloride.

LC/MS (m/z) 315.4 (MH+); RT = 2.65

86: *N-[5-(5-Methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide*

Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and acetyl chloride.

LC/MS (m/z) 301.3 (MH+); RT = 2.28

87: *2,2-Dimethyl-N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide*

Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and 2,2-dimethyl-propionyl chloride.
LC/MS (m/z) 343.4 (MH+); RT = 3.27

88: *N-[5-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2,2-dimethyl-propionamide*
Prepared from 5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and 2,2-dimethyl-propionyl chloride.
LC/MS (m/z) 357.4 (MH+); RT = 3.46

89: *2,2-Dimethyl-N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-propionamide*
Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and 2,2-dimethyl-propionyl chloride.
LC/MS (m/z) 343.4 (MH+); RT = 3.07

90: *Furan-3-carboxylic acid [5-(2-methyl-2H-tetrazol-5-yl)-4-(4H-1lambda*4*-thiophen-2-yl)-thiazol-2-yl]-amide*
Prepared from 5-(2-methyl-2H-tetrazol-5-yl)-4-thiophen-2-yl-thiazol-2-ylamine and furan-3-carbonyl chloride.
LC/MS (m/z) 361.4 (MH+); RT = 2.75

91: *Thiophene-3-carboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide*
Prepared from 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-ylamine and thiophene-3-carbonyl chloride.
LC/MS (m/z) 369.4 (MH+); RT = 3.18

92: *Thiophene-3-carboxylic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide*

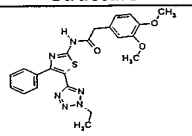
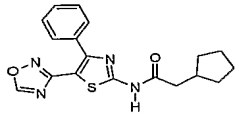
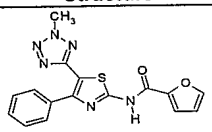
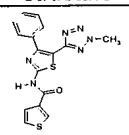
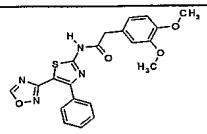
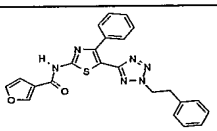
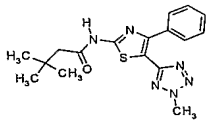
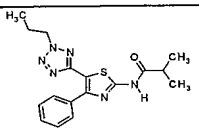
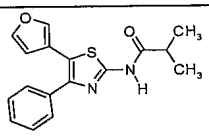
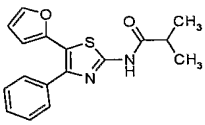
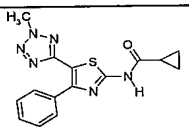
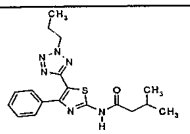
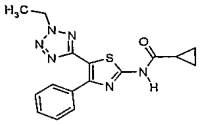
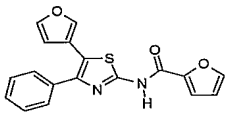
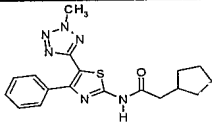
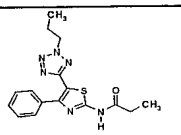
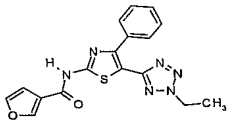
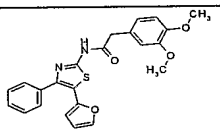
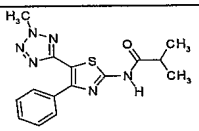
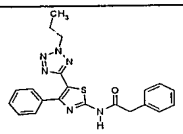
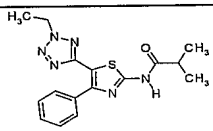
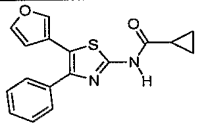
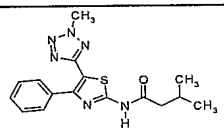
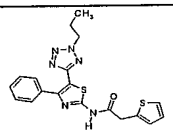
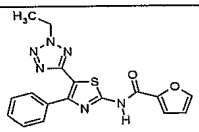
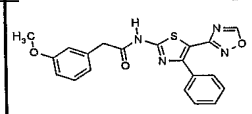
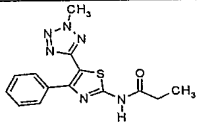
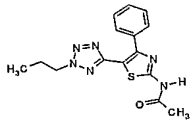
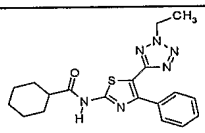
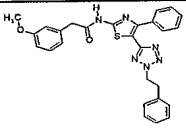
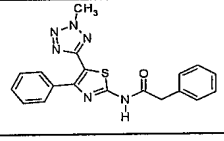
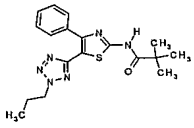
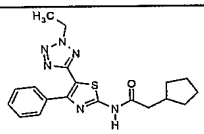
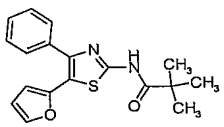
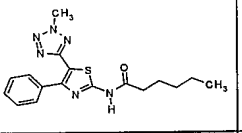
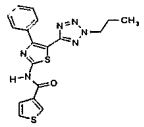
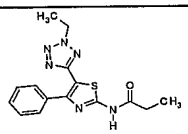
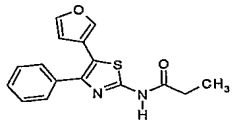
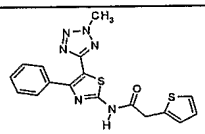
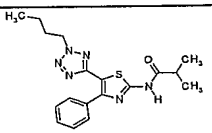
Prepared from 5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-ylamine and thiophene-3-carbonyl chloride.

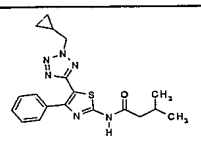
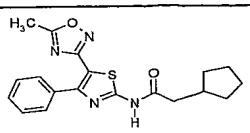
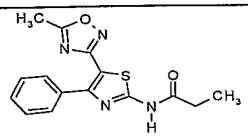
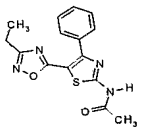
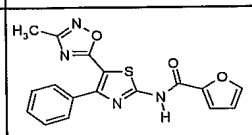
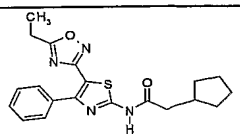
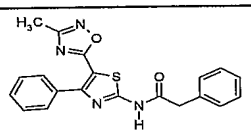
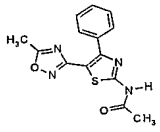
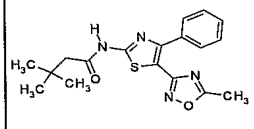
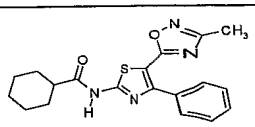
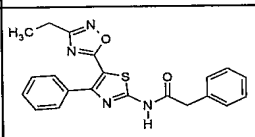
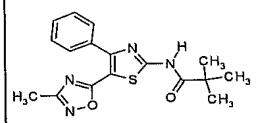
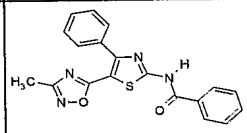
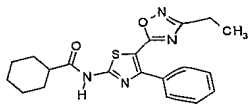
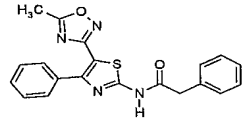
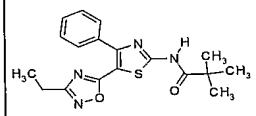
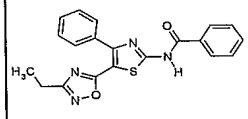
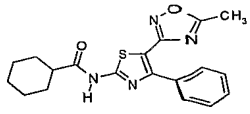
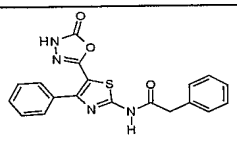
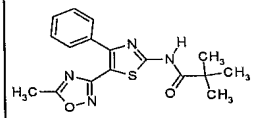
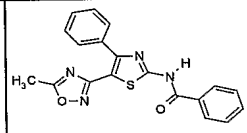
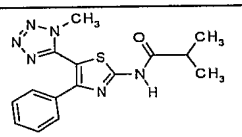
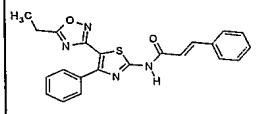
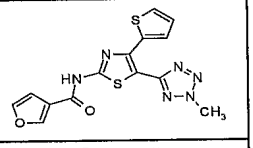
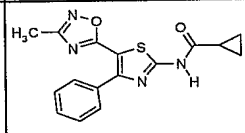
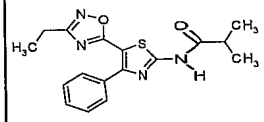
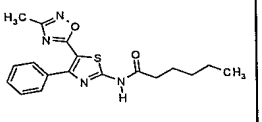
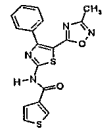
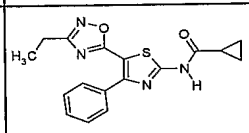
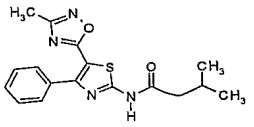
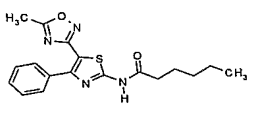
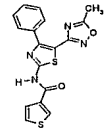
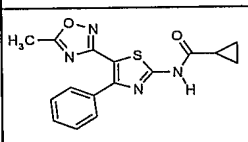
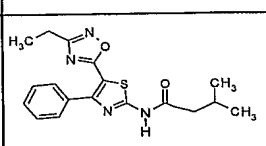
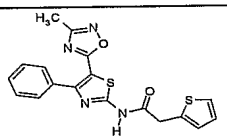
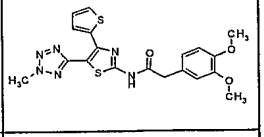
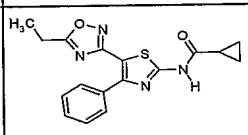
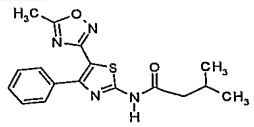
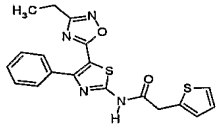
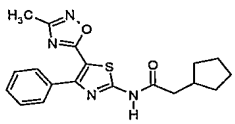
LC/MS (m/z) 369.4 (MH+); RT = 3.01

93: *2-(3,4-Dimethoxy-phenyl)-N-[5-(2-methyl-2H-tetrazol-5-yl)-4-thiophen-2-yl-thiazol-2-yl]-acetamide*

Prepared from 5-(2-methyl-2H-tetrazol-5-yl)-4-thiophen-2-yl-thiazol-2-ylamine and (3,4-dimethoxy-phenyl)-acetyl chloride.

LC/MS (m/z) 445.5 (MH+); RT = 2.69

No.	Structure	No.	Structure	No.	Structure	No.	Structure
1		13		25		37	
2		14		26		38	
3		15		27		39	
4		16		28		40	
5		17		29		41	
6		18		30		42	
7		19		31		43	
8		20		32		44	
9		21		33		45	
10		22		34		46	
11		23		35		47	
12		24		36		48	

No.	Structure	No.	Structure	No.	Structure	No.	Structure
49		61		73		85	
50		62		74		86	
51		63		75		87	
52		64		76		88	
53		65		77		89	
54		66		78		90	
55		67		79		91	
56		68		80		92	
57		69		81		93	
58		70		82			
59		71		83			
60		72		84			

Pharmacological Testing

The compounds of the invention were tested according to the following methods:

A_{2A} efficacy assays

Cloning of the human cDNA encoding the A_{2a} receptor.
cDNA was obtained by random primed reverse transcription of human fetal brain RNA (Clonetech). A subsequent polymerase chain reaction (PCR) was performed using the cDNA as template and the oligonucleotides TTTACGCGTGGCCATGCCCATCATGGGCTCCTC and TTTCTAGAATCAGGACACTCCTGCTCCATC as primers for the amplification. The amplification was performed using Pfu polymerase (Stratagene, in accordance with the manufactures recommendation) with an annealing temperature of 54°C. The reaction mixture was analyzed by an agarose gel electrophoresis and a band of 1.2 kb was excised and the DNA eluded. The eluded DNA was digested with the restriction enzymes MluI and XbaI and ligated into a vector, pCIneo, cut with the same enzymes. DNA was isolated and sequenced. CHO cells was transfected with the pCIneo clone expressing the A_{2a} receptor and cells with stable integration of the plasmids were isolated after 2-3 weeks growth in the presence of either 5 mg/ml or 10mg/ml G418.

CHO cells transfected with A_{2A} receptors as described above were grown in F12 nutrient mixture (kaighs modification, Life technologies) with 10% FCS, 1% glutamin and 1% penicillin/streptomycin and 1 mg/mL G418.

24 h prior to assay performance, 10000 cells/well were seeded in costar 96-well plates in media without G418 to 60-80% confluence. The cells were stimulated with NECA (00-9498, final concentration 75 nM) corresponding to about 80% agonist efficacy.

The cell media was removed and the cells washed 3 times in 37 °C pre-equilibrated PBS and incubated (on shaker) with 10 µL of a suspension of acceptor beads and 10µL of a solution of test compound or standard compound (0-10 µM) in darkness for 30 min at 25 °C before addition of 30 µl of a suspension of donor beads and further

incubation 60-120 min in darkness. The plates were analysed according to manufacturers instruction (Alpha screen, Perkin Elmer (Pachard Biosciense)).

The acceptor beads were suspended in a stimulation buffer (5 mM HEPES, 0.1 % BSA in Hanks balanced salt pH 7.4 w/o phenol red (Gibco). The donor beads were suspended in a lysis buffer (the stimulation buffer with 0,3% Tween 20 and biotinylated cAMP) according to manufacturers instruction (Alpha screen, Perkin Elmer (Pachard Biosciense)).

The data were fitted with non-linear regression, and IC_{50} and K_i values were calculated from the equations:

$IC_{50} = ([I]/ (100/(100-\%INH))/(1+([ag]/EC_{50})$

and

$K_i = IC_{50}/(1-[ag]/EC_{50})$,

where [I] is the inhibitor concentration, [ag] is the assay agonist concentration and EC_{50} is the agonist concentration required for half maximal effect.

A_{2A} binding assay:

Membrane preparations for A_{2A} binding analysis:

Expression in insect cells

The human A_{2a} encoding DNA were excised from the pCIneo constructs by MluI and XbaI and subcloned into the pFASTBAC2 vector cut with XbaI and BssHII. The inserts were recombined into the baculo vector using the Bac-to-Bac® system (Invitrogen). The generation and isolation of baculo virus was performed as described by the distributor (Invitrogen). High Five cells (Invitrogen) was grown at 27°C in suspension to a density of $1*10^6$ and infected with a MOI of 0.5. The cells are harvested 72 h post infection and membranes prepared.

High five cells expressing A_{2A} receptors were homogenized in 50 mM tris-buffer pH 7.4 in an ultra Turrax homogenisator. The membranes were diluted to a concentration of 0.6 mg/ml and 2U Adenosine deaminase (Roche)/ml membrane suspension was added. The solution was preincubated 30 min at 37 °C before use.

A_{2A} binding analysis:

Binding assay was performed in 96 well flat bottom plate and initiated by mixing 10.6 µg protein/well with solutions of standard compounds or test compounds (final concentrations 0-10 µM) and 1 nM final concentration of ^{3}H-ZM241385 (R1036 from Tocris). All test compounds were diluted in 50 nM trisbuffer from DMSO-stocks (2 mM or 10 mM). The reactions (final volume = 200 µL) were incubated for 30 min at 25 °C and washed on Unifilter-GF/B with water. The filters were dried 20 min (37 °C) before addition of 35 µl Microscient-0 or Optiphase supermix and counting in a Trilux counter for 1 min.

The data were fitted with non-linear regression, and IC_{50} and K_i values were calculated from the equations :

$IC_{50} = ([I]/ (100/(100-\%INH))/(1+([L]/K_D)$

and

$K_i = IC_{50}/(1-[L]/K_D)$,

where [I] is the inhibitor concentration, and [L] and K_D are concentration and dissociation equilibrium constant of the radiotracer, respectively.

The exemplified compounds 1-93 of the invention are A_{2A}-receptor ligands, such as antagonists, agonists, reverse agonists or partial agonists having a human A_{2A} binding affinity (K_i) of 210 nM or less.

Formulation Examples

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilising the solution and filling it in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulation of the invention are as follows:

2) Tablets containing 5.0 mg of a compound of the invention calculated as the free base:

Compound **1**	5.0 mg
Lactose	60 mg
Maize starch	30 mg
Hydroxypropylcellulose	2.4 mg
Microcrystalline cellulose	19.2 mg
Croscarmellose Sodium Type A	2.4 mg
Magnesium stearate	0.84 mg

2) Tablets containing 0.5 mg of a compound of the invention calculated as the free base:

Compound **1**	0.5 mg
Lactose	46.9 mg
Maize starch	23.5 mg
Povidone	1.8 mg
Microcrystalline cellulose	14.4 mg

Croscarmellose Sodium Type A	1.8 mg
Magnesium stearate	0.63 mg

3) Syrup containing per millilitre:

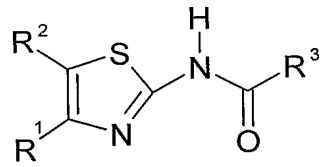
Compound **1**	25 mg
Sorbitol	500 mg
Hydroxypropylcellulose	15 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 mL
Flavour	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 mL

4) Solution for injection containing per millilitre:

Compound **1**	0.5 mg
Sorbitol	5.1 mg
Acetic Acid	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 mL

Claims

1. A compound of formula I



I

wherein R^1 is phenyl, thien-2-yl or thien-3-yl, wherein each phenyl and thienyl optionally are substituted with one or more substituents selected from halogen, C_{1-6}-alkyl and C_{1-6}-alkoxy;

R^2 is a five membered heteroaryl selected from the group consisting of furan-2-yl, furan-3-yl, [1,2,4]-oxadiazol-3-yl, [1,2,4]-oxadiazol-5-yl, [1,2,5]-oxadiazol-3-yl, [1,2,4]-thiadiazol-3-yl, [1,2,4]-thiadiazol-5-yl, [1,2,5]-thiadiazol-3-yl, wherein the heteroaryl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkoxy-C_{1-6}-alkyl, or R^2 is tetrazol-5-yl substituted in the 1 or 2-position with C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl, or R^2 is 5-oxo-4,5-dihydro-[1,3,4]-oxadiazol-2-yl;

and R^3 is selected from the group consisting of C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, furanyl, furanyl-C_{1-6}-alkyl, thienyl, thienyl-C_{1-6}-alkyl, phenyl, phenyl-C_{2-6}-alkene and phenyl-C_{1-6}-alkyl wherein the phenyl-C_{1-6}-alkyl optionally is substituted in the phenyl ring with one or more substituents selected from halogen, C_{1-6}-alkyl and C_{1-6}-alkoxy;

for use as a medicament.

2. A compound according to claim 1 wherein R^1 is phenyl, for use as a medicament.

3. A compound according to claim 1 wherein R^1 is thien-2-yl, for use as a medicament.

4. A compound according to any of claims 1-3 wherein if R^2 is a tetrazol-5-yl, then it is substituted in the 2-position, for use as a medicament.

5. A compound according to any of claims 1-3 wherein if R^2 is a tetrazol-5-yl, then it is substituted in the 1-position, for use as a medicament.

6. A compound according to any of claims 1-5 wherein if R^2 is a tetrazol-5-yl, then it is substituted with methyl, ethyl, propyl, butyl, isobutyl, cyclopropanmethyl or phenethyl, for use as a medicament.

7. A compound according to any of the claims 1-3 wherein R^2 is furan-2-yl or furan-3-yl, wherein the heteroaryl is optionally substituted with on or more substituents selected from the group consisting of C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkoxy-C_{1-6}-alkyl, for use as a medicament.

8. A compound according to any of the claims 1-3 wherein R^2 is [1,2,4]-oxadiazol-3-yl, wherein the heteroaryl is optionally substituted with on or more substituents selected from the group consisting of C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkoxy-C_{1-6}-alkyl, for use as a medicament.

9. A compound according to any of the claims 1-3 wherein R^2 is [1,2,4]-oxadiazol-5-yl, wherein the heteroaryl is optionally substituted with on or more substituents selected from the group consisting of C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkoxy-C_{1-6}-alkyl, for use as a medicament.

10. A compound according to any of the claims 1-3 wherein R^2 is [1,2,5]-oxadiazol-3-yl, wherein the heteroaryl is optionally substituted with on or more substituents selected from the group consisting of C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkoxy-C_{1-6}-alkyl, for use as a medicament.

11. A compound according to any of the claims 1-3 wherein R^2 is 5-oxo-4,5-dihydro-[1,3,4]-oxadiazol-2-yl, for use as a medicament.

12. A compound according to any of claims 1-11 wherein R^3 is selected from the group consisting of C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkylmethyl, furan-2-yl, furan-3-yl, thien-2-yl, thien-2-yl-methyl, thien-3-yl, phenylmethyl, phenethylene and benzyl optionally substituted in the phenyl ring, for use as a medicament.

13. A compound according to claim 12 wherein the benzyl is substituted with one or two methoxy groups in the phenyl ring, for use as a medicament.

14. A compound according to any of claims 12 or 13 wherein the benzyl is substituted in the 3 and/or 4 position of the phenyl ring, for use as a medicament.

15. A compound according to claim 1 selected from the group consisting of:
2-(3,4-Dimethoxy-phenyl)-*N*-[5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
2-(3,4-dimethoxy-phenyl)-*N*-(5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-acetamide,
N-(5-furan-3-yl-4-phenyl-thiazol-2-yl)-isobutyramide,
cyclopropanecarboxylic acid [5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
furan-3-carboxylic acid [5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
N-[5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,
furan-2-carboxylic acid [5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
cyclohexanecarboxylic acid [5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
2-cyclopentyl-*N*-[5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
N-[5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,
cyclopropanecarboxylic acid (5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-amide,
thiophene-3-carboxylic acid [5-(2-ethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
2-cyclopentyl-*N*-(5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-acetamide,

furan-3-carboxylic acid [5-(2-phenethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

N-(5-furan-2-yl-4-phenyl-thiazol-2-yl)-isobutyramide,

furan-2-carboxylic acid (5-furan-3-yl-4-phenyl-thiazol-2-yl)-amide,

2-(3,4-dimethoxy-phenyl)-*N*-(5-furan-2-yl-4-phenyl-thiazol-2-yl)-acetamide,

cyclopropanecarboxylic acid (5-furan-3-yl-4-phenyl-thiazol-2-yl)-amide,

2-(3-methoxy-phenyl)-*N*-(5-[1,2,4]oxadiazol-3-yl-4-phenyl-thiazol-2-yl)-acetamide,

2-(3-methoxy-phenyl)-*N*-[5-(2-phenethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,

N-(5-furan-2-yl-4-phenyl-thiazol-2-yl)-2,2-dimethyl-propionamide,

N-(5-furan-3-yl-4-phenyl-thiazol-2-yl)-propionamide,

N-[5-(2-phenethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,

N-(5-furan-2-yl-4-phenyl-thiazol-2-yl)-propionamide,

furan-2-carboxylic acid [5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

3,3-dimethyl-*N*-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-butyramide,

cyclopropanecarboxylic acid [5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

2-cyclopentyl-*N*-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,

N-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,

3-methyl-*N*-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-butyramide,

N-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,

N-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide,

hexanoic acid [5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

N-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide,

N-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,

2,2-dimethyl-*N*-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,

thiophene-3-carboxylic acid [5-(2-methyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

N-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-isobutyramide,

3-methyl-*N*-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-butyramide,

N-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-propionamide,

2-phenyl-*N*-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-acetamide,

N-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-2-thiophen-2-yl-acetamide,

N-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-acetamide,
2,2-dimethyl-*N*-[4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-propionamide,
thiophene-3-carboxylic acid [4-phenyl-5-(2-propyl-2*H*-tetrazol-5-yl)-thiazol-2-yl]-amide,
N-[5-(2-butyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,
2-cyclopentyl-*N*-[5-(2-isobutyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
N-[5-(2-isobutyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide,
N-[5-(2-cyclopropylmethyl-2*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-3-methyl-butyramide,
furan-2-carboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
3,3-dimethyl-*N*-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-butyramide,
N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-benzamide,
N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-benzamide,
N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-benzamide,
cyclopropanecarboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
cyclopropanecarboxylic acid [5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
cyclopropanecarboxylic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide,
cyclopropanecarboxylic acid [5-(5-ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide,
2-cyclopentyl-*N*-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
2-cyclopentyl-*N*-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,
2-cyclopentyl-*N*-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide,
2-cyclopentyl-*N*-[5-(5-ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide,
cyclohexanecarboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

cyclohexanecarboxylic acid [5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

cyclohexanecarboxylic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide,

N-[5-(1-methyl-1*H*-tetrazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,

N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-isobutyramide,

3-methyl-*N*-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-butyramide,

N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-3-methyl-butyramide,

3-methyl-*N*-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-butyramide,

N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,

N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,

N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-propionamide,

N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide,

N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide,

N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide,

N-[5-(5-Oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-4-phenyl-thiazol-2-yl]-2-phenyl-acetamide,

2-(3,4-dimethoxy-phenyl)-*N*-[5-(2-methyl-2*H*-tetrazol-5-yl)-4-thiophen-2-yl-thiazol-2-yl]-acetamide,

N-[5-(5-ethyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-3-phenyl-acrylamide,

hexanoic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,

hexanoic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide,

N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide,

N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide,

N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-2-thiophen-2-yl-acetamide,

N-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,

N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-acetamide,

N-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-acetamide,

2,2-dimethyl-*N*-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-propionamide,

N-[5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-2,2-dimethyl-propionamide,
2,2-dimethyl-*N*-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-propionamide,
furan-3-carboxylic acid [5-(2-methyl-2*H*-tetrazol-5-yl)-4-thiophen-2-yl-thiazol-2-yl]-amide,
thiophene-3-carboxylic acid [5-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-phenyl-thiazol-2-yl]-amide,
thiophene-3-carboxylic acid [5-(5-methyl-[1,2,4]oxadiazol-3-yl)-4-phenyl-thiazol-2-yl]-amide,for use as a medicament.

16. Use of a compound of formula I wherein R^1, R^2 and R^3 are as defined in any one of claims 1-15 for the manufacture of a medicament for treatment of a disease where an A_{2A}-receptor is implicated.

17. Use of a compound according to claim 16 wherein the disease where an A_{2A}-receptor is implicated, is selected from the group consisting of Parkinson's Disease, Alzheimer´s Disease, Huntington´s disease, epilepsia, cerebral ischemia, haemorrhagic stroke, neonatal ischemia and hypoxia, subarachnoid haemorrhage, traumatic brain injury, brain damage following cardiac arrest, and for the treatment of depression and psychosis disorders.

18. Use of a compound according to claim 17 wherein the disease where an A_{2A}-receptor is implicated, is Parkinson's disease.

19. A compound of formula I wherein R^1, R^2 and R^3 are as defined in any one of claims 1-15, provided that the compound is not *N*-[5-(5-nitro-furan-2-yl)-4-phenyl-thiazol-2-yl]-benzamide.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2005/000591

A. CLASSIFICATION OF SUBJECT MATTER
C07D417/04 C07D417/14 A61K31/427 A61P25/02 A61P25/16
A61P25/18 A61P25/24 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/053982 A1 (PRESS NEIL JOHN ET AL) 18 March 2004 (2004-03-18) the whole document	1,16
A	MUIJLWIJK-KOEZEN VAN J E ET AL: "Thiazole and Thiadiazole Analogues as a Novel class of Adenosine Receptor Antagonists" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, no. 5, 1 March 2001 (2001-03-01), pages 749-762, XP002318825 ISSN: 0022-2623 cited in the application the whole document	1,16

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2005	23/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Megido, B

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2005/000591

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/64418 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH; HENG, R) 16 December 1999 (1999-12-16) the whole document	1,16

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK2005/000591

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 2004053982 A1	18-03-2004	AT	300536 T	15-08-2005
		AU	3722102 A	03-06-2002
		BR	0115478 A	17-02-2004
		CA	2429442 A1	30-05-2002
		CN	1476447 A	18-02-2004
		CZ	20031393 A3	13-08-2003
		DE	60112322 D1	01-09-2005
		WO	0242298 A1	30-05-2002
		EP	1339711 A1	03-09-2003
		HU	0302079 A2	29-09-2003
		JP	2004521871 T	22-07-2004
		MX	PA03004439 A	19-08-2003
		NO	20032277 A	21-07-2003
		NZ	525875 A	26-11-2004
		PL	361842 A1	04-10-2004
		SK	6032003 A3	08-01-2004
		ZA	200303721 A	10-05-2004
WO 9964418 A	16-12-1999	AU	4506399 A	30-12-1999